



CASE REPORT

Fraser syndrome: Phenotypic variability and unusual findings in four Egyptian families



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Abstract *Background and aim:* Fraser syndrome (FS) is a rare autosomal recessive disorder characterized by cryptophthalmos, cutaneous syndactyly, laryngeal malformations and urogenital defects. It may be also associated with ear, nose and skeletal abnormalities. There is a marked inter-familial clinical variability. However, there is strong phenotypic similarity and concordance of the degree of severity of the disease within a family. Our aim was to report new cases of FS from the Egyptian population.

Patients and methods: The study was carried out on 6 new cases of FS from four Egyptian families. All patients satisfied the diagnostic criteria for FS.

Results: Cryptophthalmos and ambiguous genitalia were each present in 5/6 of the studied cases, while syndactyly and urinary tract abnormalities were found in 4/6 of them. Nasal anomalies, sclerocornea and abnormal hair growth pattern were constant features observed in 100% of the cases. The frequency of additional anomalies in our series was also higher than those previously reported as umbilical abnormalities and contractures of large joints.

Conclusion: In conclusion, our findings add further evidence for the clinical variability associated with FS. The studied cases showed inconsistent compatibility with life and variable expressions in prenatal sonographic findings and postnatal clinical manifestations.

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1. Introduction

Fraser syndrome (FS; cryptophthalmos–syndactyly syndrome; OMIM #219000) is a rare autosomal recessive multiple malformation syndrome characterized by variable expressions of cryptophthalmos, syndactyly, abnormal genitalia, malformations of the nose, ear and larynx, renal agenesis and umbilical hernia [1]. Uncommon manifestations include cleft lip and/or palate, cardiac malformations, musculoskeletal anomalies, and mental retardation in survivors [2].

Abbreviations: FS, Fraser syndrome; IUGR, intrauterine growth retardation

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About 20 years after the first description of the syndrome by Fraser [3] and Thomas et al. [1] reviewed 124 cases of cryptophthalmos and associated syndromes and established minimal diagnostic criteria clearly separating FS from isolated cryptophthalmos. 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. The major criteria comprise cryptophthalmos, syndactyly, abnormal genitalia or a sib with FS, while the minor criteria comprise congenital malformations of nose, ears, or larynx, cleft lip \pm palate, skeletal defects, umbilical hernia, renal agenesis or mental retardation. Some of the most characteristic malformations of the FS occur in areas that remain temporarily fused in utero: the eyelids, the digits, and the vagina. Since separation of the eyelids and digits involves a process of controlled necrosis, Thomas et al. [1] had speculated about a defect in programmed cell death.

In 2007, van Haelst et al. [2] provided a revision of the diagnostic criteria for FS according to Thomas et al. through the addition of airway tract and urinary tract anomalies to the major criteria and removal of mental retardation and clefting as criteria. Their proposed major criteria, thus, included syndactyly, cryptophthalmos spectrum, urinary tract abnormalities, ambiguous genitalia, laryngeal and tracheal anomalies, and positive family history. Minor criteria included anorectal defects, dysplastic ears, skull ossification defects, umbilical abnormalities, and nasal anomalies. van Haelst et al. [2] suggested that the diagnosis of FS can be made if either 3 major criteria, or 2 major and 2 minor criteria, or 1 major and 3 minor criteria are present in a patient.

Mutations in *FRAS1* and *FREM2* genes, which belong to a family of large extracellular matrix proteins, are well-established causes of FS [4,5] and together they account for the majority of cases [6]. More recently, mutations in *GRIP1* gene have also been identified to cause FS in humans [7]. The potential involvement of several other genes such as *Hemicentin1* (*HMCN1*), *Furin*, and *Fibulin 1*, that interact in basement membrane anchorage, has been proposed suggesting further genetic heterogeneity [8,9].

Although considered rare, the exact prevalence of FS, however, is not known. A recent epidemiological study reported an approximate estimated prevalence of 1:500,000 births [10]. Herein we report on six new cases of FS, including two sib pairs, from four Egyptian families. The described cases manifest variability in clinical findings and compatibility with life from a surviving and thriving infant into perinatal death or intrauterine fetal demise.

2. Clinical report

2.1. Family 1

A 6-month-old female infant [case 1-1] presented with cryptophthalmos and absent vaginal orifice. She was the second child of healthy Egyptian consanguineous parents after a healthy boy. On examination, the patient displayed total cryptophthalmos of the left eye and absent eyebrow but the globe was felt underneath the skin. The right eye was small with upper lid coloboma and sclerocornea. Scanty scalp hair and right eyebrow, high forehead with frontal bossing, dolichocephaly, broad nasal root, depressed bridge and upturned nasal tip with a groove were also noted. The ears were small

and low set with increased helical folding, hypoplastic attached lobules and stenotic external auditory canals. An examination of extremities revealed small hands with partial cutaneous syndactyly between the third, fourth and fifth fingers of both hands and partial syndactyly between all toes of the right foot. We also noted widely spaced hypoplastic nipples, a small umbilical hernia and prominent hemangioma on the upper chest. External genitalia were hypoplastic with absent vaginal opening and clitoromegaly (Fig. 1: 1-A through E). The anthropometric measurements were normal. Echocardiography and ultrasonography of the abdomen and pelvis were unremarkable and chromosomal analysis showed normal female karyotype.

2.2. Family 2

After termination of pregnancy around 28 weeks of gestation, a male fetus [case 2-2], who died immediately after birth, was referred for genetic evaluation. The fetus was the second child of a 30-year-old healthy woman and her first-cousin husband. The pregnancy progressed uneventfully until the standard second trimester ultrasound screening revealed severe oligohydramnios and bilateral renal agenesis. Amniocentesis was performed and revealed a normal male karyotype, however, the couple opted to terminate pregnancy at 28 weeks of gestation. The first child of this couple [case 2-1], who was born at term and died soon after birth, displayed cryptophthalmia, cleft lip and ambiguous genitalia.

External examination of the fetus 2-2 was consistent with a male fetus showing striking ocular hypertelorism, complete cryptophthalmos of the right eye with absence of eye structures. Abortive cryptophthalmos (congenital symblepharon), was noted in the laterally-displaced slanted-down left eye, which also showed a hazy cornea. A bilateral tongue of scalp hair from parietal region was found to be extending on temples to the site of eyebrows. The nose was very broad, flat and asymmetric with thick alae nasi and slit like nares. The ears were malformed, small and low set with cryptotia, uplifted lobules and stenotic external auditory meatus. Complete cutaneous syndactyly of the second through fifth digits of the right hand and right foot was noted. Complete cutaneous syndactyly was also found between the third and fourth fingers of the left hand and second and third toes of the left foot. In addition, webbing of neck and axillae and a markedly low-set umbilical cord were noted (Fig. 1: 2-A through E). The fetus showed normal genitalia and the growth parameters were within the average for age.

2.3. Family 3

A non-consanguineous couple was referred for genetic counseling after termination of pregnancy because of an abnormal ultrasound scan revealing anhydramnios, bilateral renal agenesis, non-visualization of urinary bladder, intrauterine growth retardation (IUGR) and single umbilical artery at 24 weeks' gestation. This pregnancy was the ninth for the parents after 7 first trimester abortions and a full term pregnancy that resulted in a stillborn male baby [case 3-1] with absent kidneys, cryptophthalmia and microtia.

Post-mortem examination of the fetus [case 3-2] showed marked hypertelorism, partial cryptophthalmos of the right



Figure 1 Clinical features of Egyptian cases of FS. *Case 1-1*: Complete cryptophthalmos of Lt eye with absent eyebrow, upper lid coloboma and sclerocornea of Rt eye, scanty scalp hair, high forehead with frontal bossing, broad nasal root and grooved nasal tip [1-A], prominent hemangioma on upper chest [1-B], partial cutaneous syndactyly between 3rd and 5th fingers [1-C], partial syndactyly between all toes of the right foot [1-D], clitoromegaly with hypoplastic labia and absent vaginal opening [1-E]. *Case 2-2*: Striking ocular hypertelorism, complete cryptophthalmos of Rt eye, abortive crypto-phththalmos and slanting down of Lt eye, bilateral tongue of scalp hair from parietal region extending to the site of eyebrows, very broad asymmetric nose with thick alae nasi and slit like nares and uplifted ear lobules [2-A], small Lt ear with cryptotia and stenotic external auditory meatus [2-B], complete cutaneous syndactyly between 3rd and 4th fingers of Lt hand [2-C], complete cutaneous syndactyly of 2nd through 5th digits of the Rt foot [2-D], a markedly low-set umbilical cord [2-E]. *Case 3-2*: Hirsutism of the forehead with the anterior hairline extending almost to the site of eyebrows, hypertelorism, coloboma of Rt upper eyelid and absence of eyelashes and Rt eyebrow, abortive cryptophthalmos of Lt eye with absent eyelashes, slanting-down palpebral fissure and cloudy cornea, broad nose with broad columella and narrow nostrils and low-set ears [3-A], axillary web [3-B], camptodactyly of all fingers [3-C], long toes [3-D], low insertion of umbilical cord and abnormal male genitalia [3-E]. *Case 4-1*: Abnormal skull with aberrant hair growth with the scalp hair extending forward over the forehead, puffy eyelids, abnormal eyebrows, long eyelashes, bilateral sclerocornea, pinched nose, severe micro-retrognathia [4-A and B], extensive cutaneous syndactyly between 2nd through 5th fingers of Rt hand [4-C], rocker bottom heels and complete cutaneous syndactyly between Rt 2nd through 5th toes and between all toes on the Lt side [4-D], abnormal genitalia and anteriorly-displaced anus [4-E].

eye with coloboma of the upper eyelid and absence of eyelashes and the right eyebrow. The left eye had abortive cryptophthalmos with hypoplastic eyelids, absent eyelashes, slanting-down palpebral fissure and cloudy cornea. There was hirsutism of the forehead with the anterior hairline extending almost to the site of eyebrows. The ears displayed cryptotia and low setting. The nose was broad, depressed with a broad columella and narrow nostrils. Camptodactyly of all fingers was noticed while the toes were normal. We also noted neck, axillary and crural webbing, low insertion of umbilical cord and abnormal male genitalia (Fig. 1: 3-A through E).

2.4. Family4

A 21-year-old healthy primigravida, was referred for genetic evaluation after a routine mid-trimester ultrasound scan had revealed IUGR, severe lung hypoplasia, bilateral renal agenesis and oligohydramnios. Termination of pregnancy was done at 24th week of gestation and the fetus [case 4-1] was subjected to karyotyping and postmortem clinical examination. The affected fetus showed turricephaly, a skull defect and aberrant frontolateral hair growth with the scalp hair extending forward over the forehead and temples onto the lateral cheeks. Other

facial abnormalities included puffy eyelids, abnormal eyebrows, long eyelashes, bilateral sclerocornea, pinched nose, striking micro-retrognathia and low-set dysplastic ears. Extensive soft-tissue syndactyly was found between second through fifth fingers of both hands, between second through fifth toes of the right foot and between all toes on the left side. Rocker

bottom heels, abnormal genitalia, anteriorly-displaced anus and multiple webbings; axillary, cubital and crural, were also noted (Fig. 1: 4-A through E).

The demographic, clinical and sonographic findings in the six cases of FS included in the present study are summarized in Table 1. The frequency of congenital anomalies detected

Table 1 Demographic, clinical and prenatal sonographic features of our 6 cases in comparison to the diagnostic criteria for Fraser syndrome according to van Haelst et al. [2].

	1-1	2-1	2-2	3-1	3-2	4-1	Frequency
Sex	F	M [†]	M	M [†]	M	F	
Consanguinity	+	+	+	-	-	-	
Compatibility with life	Survival into infancy	Perinatal death	TOP 28 ws.	Stillborn	TOP 24 ws.	TOP 24 ws.	
<i>Major criteria</i>							
Cryptophthalmos	+	+	+	+	+	-	5/6
Syndactyly	+	+	+	-	-	+	4/6
Abnormal genitalia	+	+	-	+	+	+	5/6
Urinary tract abnormalities	-	-	+	+	+	+	4/6
Laryngeal and tracheal anomalies	-	-	-	-	-	-	0/6
Sib with Fraser syndrome	-	-	+	-	+	-	
<i>Minor criteria</i>							
Anorectal defects	-	-	-	-	-	-	0/6
Dysplastic ears	+	?	+	+	+	+	5/5
Skull ossification defects	-	-	-	?	-	+	1/5
Nasal anomalies	+	+	+	+	+	+	6/6
Umbilical abnormalities	+	?	+	+	+	-	4/5
<i>Uncommon features</i>							
Cleft lip ± palate	-	+	-	-	-	-	1/6
Cardiac malformations	-	-	-	-	-	-	0/6
Sclerocornea (corneal clouding)	+	+	+	+	+	+	6/6
Contractures of large joints (multiple pterygia)	-	?	+	?	+	+	3/4
Abnormal hair growth pattern	+	+	+	+	+	+	6/6
IUGR	-	+	-	+	+	+	4/6
Others	Hemangioma	-	-	-	Camptodactyly	Micrognathia	
Intellectual disability	NA	NA	NA	NA	NA	NA	
Prenatal US findings	ND	ND	Oligohydramn.-bil. renal agenesis	ND	Oligohydramn.-bil. renal agenesis-IUGR-single umbil. artery	IUGR-lung hypoplasia, bil. renal agenesis-oligohydramn.	
Normal karyotyping	+	ND	+	ND	+	+	

ND, not done.

NA, not applicable.

“?” We failed to recognize some features in the probands’ sibs for whom a reliable clinical description was lacking and no illustrative pictures were available.

† Cases in the shaded columns were not clinically examined by the authors. The described features are according to sonographic findings, photos and neonatologists’ reports.

in the studied FS patients is shown in the last column of the table. The findings are also illustrated in Fig. 1. All patients fulfilled the criteria for the diagnosis of FS as formulated by van Haelst et al. [2].

3. Discussion

In this report, we describe the clinical manifestations of six cases of FS from four Egyptian families. FS is considered a very rare congenital malformation syndrome. Most cases of FS are still-born or die within the first year of life and death is usually secondary to renal agenesis and laryngeal stenosis [11–13]. Additionally, and due to the wide use of antenatal screening services, a high proportion of FS pregnancies; particularly the severe ones associated with bilateral renal agenesis, is expected to be terminated. All these factors brought together will reduce the prevalence of the syndrome and add to its rarity. Based on data provided by the European Surveillance of Congenital Anomalies (EUROCAT) network of birth defect registries, only 26 cases of FS were identified in a population of 12,886,464 births during two decades [10]. The number of FS cases gathered in this study, thus, reflects a substantial single-center contribution.

As an autosomal recessive disorder, the parents of FS affected children are sometimes, but not always consanguineous. Our data confirm a high incidence of consanguinity (50%) in families with FS, which is almost twofold the consanguinity rate recorded for the Egyptian population [14]. It is much higher than the 15% incidence that was found in the original series of FS patients [1]. However, van Haelst et al. [2] reported a very high consanguinity rate (25/40 families) and explained it by an ascertainment bias.

Among our cohort, two families experienced recurrence of the condition. Although multiple malformations were diagnosed in the previous sibs, a definitive diagnosis of FS was missing. It was only established when the families were referred for genetic evaluation. Establishing the diagnosis will allow to offer a better genetic counseling, anticipate complications, render advice on prognosis and, most important, to offer careful screening of future pregnancies. Although there is a marked interfamilial clinical heterogeneity of FS, a strong phenotypic similarity within a family has been reported [2]. This applies to the present series as the intrafamilial variability was remarkably low in the two studied sib pairs (Table 1). However, families with multiple cases of FS showing clinical heterogeneity have been uncommonly reported [15,16].

Since its first description by Fraser in 1962 [3], the diagnostic criteria of this rare syndrome have been subjected to several revisions [1,2]. Almost all the previous studies on FS agreed that there was a marked clinical variability and that none of the major criteria were mandatory for diagnosis. Cryptophthalmos is not necessary for the diagnosis of FS but it, certainly, constitutes the most characteristic feature of the syndrome [2,10]. It is the most frequent feature but was not always present [13]. However, the rate of cryptophthalmos recorded in this study (83.3%) was similar to most of the previous reports [1,2,10]. A wide variability of this anomaly was observed in our cases ranging from complete to incomplete or abortive (congenital symblepharon variant) cryptophthalmos to lid coloboma. The term ‘cryptophthalmos–coloboma–symblepharon anomaly’ has been recently advocated to be used instead of cryptophthalmos [17].

Syndactyly of variable severity was present in 75% (4/6) of our cases. This frequency concurs with some earlier reports [10], but it is lower than the 95% frequency reported by van Haelst et al. 2007 [2]. Urinary tract anomalies were also present in 75% of the cases compared to 84%, 93% and 75% reported by Thomas et al. [1], van Haelst et al. [2], and Barisic et al. [10], respectively.

Our data pointed to a high rate of ear abnormalities, nasal anomalies, sclerocornea, abnormal hair growth patterns, multiple contractures and umbilical abnormalities. Ear malformations, nasal anomalies, sclerocornea and an abnormal hair growth pattern were constant features noted in 100% of the cases. The frequency of additional anomalies in our series was also particularly high, such as umbilical abnormalities (80%) and contractures of large joints (75%).

In this study, an abnormal frontal hairline was noted in 100% of the cases even in the absence of cryptophthalmos as in the case from family 4. Traditionally, the abnormal hair growth pattern was always associated with ocular anomalies, such as cryptophthalmos and microphthalmia, and may serve as an indicator for mal-development of the upper eyelid fold region [2]. About 40 years ago, Smith and Cohen [18] suggested that the globe was responsible for an area of hair growth suppression around the eyes, although later on Roizenblatt et al. [19] proposed that it was the eyelid that suppressed hair growth. Our findings, in particular the strikingly abnormal frontal hairline in case 4-1, may argue for further mechanisms.

Ultrasound has been an important tool in the prenatal diagnosis of malformations and most cases of FS were suspected prenatally [2]. Researchers have demonstrated the feasibility of ultrasonographic diagnosis of the FS as early as at 18 weeks’ gestation, but the findings were very inconstant [11]. In the present study, the most frequent prenatal sonographic finding was renal agenesis, accompanied by lung hypoplasia, which was encountered in all of the three fetuses subjected to antenatal scan.

The major limitation of this study was the lack of mutational analysis. As we enter the new era of genomic medicine, it is likely that a precise characterization of each patient is best accomplished by correlating genomic and phenotypic information with each other, thus enabling more accurate diagnoses. Thus, we realize that, it might not be accepted to report syndromic cases without molecular confirmation of the diagnosis. Unfortunately, there were many obstacles to attaining this goal; FS is a genetically heterogeneous disorder with causal mutations in more than three genes [4–9] and a clear phenotype–genotype relationship is not established [20]. In addition, the mutational analysis is very costly and not widely available in Egypt.

In conclusion, our findings add further evidence for the clinical variability associated with FS. The incidence of ear and nasal anomalies, abnormal hair growth patterns, contractures and umbilical abnormalities was particularly higher than that previously reported.

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Competing interests

The authors declare that they have no competing interests.

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