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TITLE PAGE

Fraser syndrome: review of literature illustrated by an historical adult case

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Abstract

Fraser syndrome (cryptophthalmos-syndactyly syndrome) is a rare autosomal recessive malformation disorder. The first description of the syndrome was reported by George Fraser in 1962. The diagnostic is based on major criteria and minor criteria established by van Haelst et al., In 2007. Unilateral or bilateral cryptophthalmos, syndactyly, unilateral renal agenesis and genital anomalies are the most frequent anomalies. Several maxillofacial, oro-dental, ear-nose-throat, hormonal and anorectal disorders are reported. Cardiac malformations, and musculoskeletal anomalies are uncommon. The syndrome id related to mutations in three different genes (FRAS1, FREM2, and GRIP1) resulting in failure of the apoptosis program and disruption of the epithelial–mesenchymal interactions during embryonic development. Prenatal diagnosis is based on detection of renal agenesis and laryngeal atresia together with a family history. Most of the fetuses with severe anomalies are terminated or resulted in stillbirth. All patient or pregnancy with a diagnosis of FS should be referred to expert centers. For the management, a collaborative approach of anesthetists, ENT, maxillofacial surgeons, geneticists is necessary. In vivo and in vitro research models are available to better understand the underlying etiology.

Introduction

Fraser syndrome (FS), also known as cryptophthalmos-syndactyly syndrome (OMIM #219000, http://omim.org/entry/219000), is an autosomal recessive malformation disorder. This Syndrome is characterized by cryptophthalmos, syndactyly, and abnormalities of the respiratory and urogenital tract[1–3]. The diagnostic is established by clinical examination and is based on major criteria (cryptophthalmos; syndactyly; ambiguous genitalia, urinary and respiratory tract anomalies and an affected sibling) and minor criteria (congenital nose and ears malformations; skull ossification defects; Anorectal anomalies and umbilical hernia)[3,4]. While FS shows an interfamilial highly variable phenotype ranging from minor symptoms to lethal malformations like renal agenesis, there is a strong phenotypic similarity exists within a family[3].

Numerous case reports of FS are published in literature since the first description of the syndromic association of cryptophtalmos-syndactily by George Fraser in 1962[1]. Most of them are clinical descriptions of fetuses from terminated pregnancy or stillbirth. The few reports of alive patients are usually pediatric cases.

Here, we provide a review of the epidemiology, the clinical presentation, the management, the physiopathology and the genetics of this syndrome especially for head and neck disorders. This review is supported by one new historical case of an adult patients with FS, never published before and managed by the maxillofacial Surgeon General Gustave Ginestet[5,6] before the first publications of FS by George Fraser in 1962.

Epidemiology and survival

FS is a rare disorder. A large epidemiological study in a European population showed a minimal estimated prevalence of 0.2 cases of FS per 100 000 births and statistically more cases in west part of Europe compared to the rest of Europe (p=0.0003)[7]. This prevalence represents a minimal estimate given that most of the fetuses with severe anomalies were terminated or resulted in stillbirth without syndrome diagnosis[7]. Regarding alive patients with FS, 25% die within the first year of life, in most cases due to airways or urinary tract anomalies[8]. Only n=3 FS patient's aged more than 20 years old are published in literature (Table1)[2,9,10]. At all, the prognosis for survival in individuals born with this condition is in general poor[11,12].

Clinical presentation and diagnosis

Diagnostic criteria

In 1986 Thomas et al., were the first authors to report the criteria establishing the diagnosis of FS[4]. In 2007, after analyzing 59 cases of FS, van Haelst and the Fraser Syndrome Collaboration Group have confirmed the clinical utility of these criteria and included the airway tract and urogenital anomalies in the major criteria whereas mental retardation and clefts were removed from this list[3] (table 2). At all, FS can be diagnosed, if two major and one minor criteria or one major and four minor criteria are present[3]. All studies agreed that there was marked clinical variability and that none of the major criteria are mandatory for diagnosis. For some authors, within a family, the phenotype and the degree of severity of the disease are strongly concordant[13].

Clinical presentation

The frequency of the most reported congenital anomalies in published Series of FS are summarized in table 3 [2–4,7,14,15]. Unilateral or bilateral cryptophthalmos, syndactyly, unilateral renal agenesis and genital anomalies are the most frequent anomalies reported in literature. Apart cryptophtalmos other maxillofacial and oro-dental findings reported are facial asymmetry, upward slanting palpebral fissures, hypertelorism, tongue of hair extending from the anterior hairline to the forehead, the eyebrows and the upper-outer edge of the orbit, broad nose and/or nasal bridge (8-84%), short neck, cleft lip and palate (11%), high arched palate (12%), malocclusion, dental crowding, fusion of primary teeth, dental hypoplasia, supragingival calculus, microdontia, retained deciduous teeth, hypodontia and short roots[2,16–18] (Figure1a and 1b). Airway disorders (laryngeal compromise) are found in 21–83% of the cases of FS[19]. Subglottic stenosis and laryngeal webs or laryngotracheal atresia are the most frequent laryngotracheal disorder. Other rare ear-nose-throat anomalies are malformed and/or low set ears, meatal stenosis or dysplastic pinna and hypoplastic notched nares or choanal stenosis or atresia [20].

FS is classed among the hormonal disorders of sex development caused by hypogonadism[21]. Reported genital anomalies are cryptorchidism and pseudo hermaphroditism for males and masculinization of the external genitalia in females with clitoral hypertrophy, vaginal atresia, labial fusion and gonadoblastoma[22,23]. Among anorectal disorders, anal atresia/stenosis are the most common. Colonic atresia, diastema of the pubic symphysis, displacement of the umbilicus and common mesentery have also been reported to illustrate abdominal anomalies associated with FS[24]. Cardiac malformations, and musculoskeletal anomalies are uncommon[7]**.** A part syndactyly, musculoskeletal abnormalities associated with FS include skull ossification defect, diastasis of the pubic symphysis, bilateral hip dysplasia and genu valgum[25].

Complementary exam

The diagnosis of FS is based on the clinical exam. Complementary exams are realized to research organ malformations. An abdominal echography is realized to investigate the urinary and genital tracts. Skull ossification defects are evaluated with radiographies and/or CT-scan (computerized tomography).

Physiopathology and genetics

FS is an autosomal recessive malformation disorder[26]. The incidence of consanguinity in families with FS is estimated reaching 15% to 30% [2,4,7,27]. This syndrome seems to be related to a failure of the apoptosis program and to the formation of large blisters during embryonic development due to defects in epidermal adhesion (disruption of the epithelial–mesenchymal interactions)[28–30]. Indeed, in embryos, the Fraser complex (FC) mediates epithelial–connective tissue interactions. This complex is composed of the Fras1/Frem family of Extra Cellular Matrix proteins[29]. These proteins have also been reported to mediate both the initiation of the mammalian kidney and glomerular maturation and integrity[31,32]. At all, Loss of expression of FC components leads to FS[33].

Mutations in three different genes (FRAS1, FREM2, and GRIP1) have been identified causing FS[34–39]. Fraser syndrome-1 (FRASRS1) is caused by homozygous or compound heterozygous mutation in the FRAS1 gene (Fraser extracellular matrix complex subunit 1, OMIM * 607830) on chromosome 4q21. At all, 27 mutations of FRAS1 gene have been reported[40,41]. Most of them are truncating mutations. The mutational spectrum includes nucleotide substitutions, splicing defects, a large insertion, small deletions/insertions and a recently reported large deletion.

Fraser syndrome-2 (FRASRS2) is caused by mutation in the FREM2 gene (FRAS1 related extracellular matrix protein 2, OMIM * 608945) on chromosome 13q13.

Fraser syndrome-3 (FRASRS3) is caused by mutation in the GRIP1 gene (glutamate receptor interacting protein, OMIM * 604597) on chromosome 12q14.

Prenatal diagnosis

Renal anomalies, syndactyly and cryptophtalmos are present in more than 90% of cases of prenatal and postnatal fetal phenotype. However, they are rarely found on prenatal ultrasound because oligohydramnios, which is frequent, hampers the prenatal recognition of the cardinal FS diagnosis criteria[42,43]. Thus, prenatal diagnosis of FS is often based on detection of some of the more easily detectable minor criteria, such as renal agenesis and laryngeal atresia, together with a family history. Aside from the presence of oligohydramnios, prenatal diagnosis can be sometimes challenging to establish especially if no previous child is affected[44,45].

The prognosis of pregnancies with FS is poor and dependent on the predominant anomalies. Termination of pregnancy may be recommended when diagnosis is made early, especially in the setting of renal agenesis or laryngeal atresia[46]. In European countries, a large proportion of pregnancies in this situation, up to 82% of cases, are medically interrupted. In all cases, prenatal diagnosis of FS should be guided by a genetic counselling[47].

Molecular diagnosis

The antenatal and post-natal diagnosis of FS could be realized by targeted sequencing of a panel of genes including FRAS1, FREM2 and GRIP1 genes[48].

Management of head and neck disorders

General management

All patient or pregnancy with a diagnosis of FS should be referred to expert centers (https://www.orpha.net/consor/cgi-bin/Clinics_Search.php?lng=EN)[47]. A Collaborative approach of experts' anesthetists, ENT, maxillofacial surgeons, geneticists is necessary.

Anesthesia

Although low incidence of complications was reported for general anesthesia in FS patients, all were related to the management of airways. Indeed, after reviewing n=125 general anesthesia for FS patients, Mathers et al., reported a high incidence (20%) of difficult or impossible tracheal intubation due to glottic stenosis[49].

Airways

Airway compromises represent a risk factor for death in infancy and early childhood, and appropriate management may be difficult due to the high incidence of recurrence, especially in the case of laryngeal webs[19,50,51]. Tracheostomy at birth could be necessary to keep the airway and preserve the patient's life[52]. In other cases, laryngotracheal alterations should be researched to anticipate a difficult/impossible intubation[53]. Direct laryngoscopy can be realized to evaluate the severity of glottic web according to Cohen's classification[54] and subglottic stenosis according to the Cotton-Myer scale[55]. Endoscopic airway measurement combining optical endoscopic instruments with open source image processing can also be useful to accurately obtain airway dimensions[56]. All cases should be personalized managed. Although no guidelines can be given due to the small number of cases published in the literature, the cricotracheal resection seems to be an adequate alternative for surgical management in glottic-subglottic stenosis and severe laryngeal webs[19].

Ophthalmic malformations

Cryptophtalmos

Cryptophthalmos, especially the eyelid defect, represents a challenge in surgical reconstruction and visual rehabilitation[57]. Saleh et al., published in 2009 a series of 13 eyes from 7 patients with FS with the aim to optimize visual potential for these patients[58]. The cryptophthalmos was complete in 3 eyes and abortive in 10 eyes. They concluded that the periocular surgical management of these type of complex cases should be planned using a systematic approach. Surgical steps should include dissection of corneal adhesions from keratinized cornea, mucous membrane graft, Mustarde eyelid switch flap with subsequent division, and further lower lid augmentation as required. Lessa et al., presented in 2011 present a two-stage surgical reconstruction procedure for correction of the upper eyelid and ocular bulb anomalies in cryptophthalmos (Mustardé's technique with fixation of the lower eyelid transposed flap to the levator muscle)[59].

Lacrimal system dysgenesis and dacryocystoceles

Syndromic congenital nasolacrimal duct obstructions are not very common in FS patients[60]. Nasal endoscopic endonasal evaluation should be realized to research dacryocystoceles and realize drainage and marsupialization if necessary[61].

<u>Dental care</u>

Self-dental cares can be difficult and/or impossible for FS patients especially when a mental retardation is present. Furthermore, cardiac abnormalities have been observed in 6 to 13% patients with FS[2,7]. Thus, FS patients have a predisposition to infective endocarditis[17].

Moreover, it seems to be an association between the presence of dental plaque, periodontal disease, and chronic lung disease (especially pneumonia). Therefore, the establishment of oral health protocols with a goal of reducing the biofilm is essential. The dentists should realize the periodontal treatment with the clinical use of chlorhexidine and Povidone-iodine (PVP-I)[62]. The rehabilitation of occlusion with for example the placement of dental implants should be favorised[18].

Research model for FS

In vivo/animal models

The bl ('blebbed') mouse model (http://omim.org/entry/219000)

In 1990, in a letter to the editors, Winter hypothesized that FS in human might be homologous to one of the mouse 'bleb' mutants phenotype[63]. Few years later in 1994, the genetic background of this 'blebbed' murine phenotype, has been more characterized by Darling and Gossler, especially the mutations in at least 5 loci, including bl[64].

Then two major events confirmed that the bl mouse is a model for FS in humans. Firstly, the screening of the DNA from bl/bl mice and the identification of a mutation in the Fras1 gene that resulting in premature protein termination[35]. Second, the demonstration that Fras1 deficiency (bl/bl homozygous embryos) results in cryptophthalmos, renal agenesis and blebbed phenotype in mice[65]. Given these elements, the authors concluded the perturbation in the composition of extracellular space underlying epithelia by loss of Fras1 function characterize the blebbed phenotype in mice and FS in humans.

Regarding the implication of GRIP1 in the FS, Takamiya et al., showed in 2004 that Grip1 is required for normal cell-matrix interactions during early embryonic development and that there is a direct functional link between the multi-PDZ domain protein GRIP1 and Fras1[66]. In 2006, Kiyozumi et al., report that Frem1 (FRAS1 related extracellular matrix protein 1, OMIM * 608944), Fras1, and Frem2 proteins are localized to the basement membrane, and that their basement membrane localization is simultaneously impaired in FS model mice (Grip1-mutant 'eye blebs' mice)[67].

The Frem2 gene was reported as a cause of FS not linked to FRAS1 by Jadeja et al., in 2005 after performing linkage analysis in the 'myelencephalic blebs' (my) mice[36]. This model showed a phenotype similar to that of Fras1-mutant mice.

At all, an article published in 2005 by Smyth and Scambler reviews the genetics of FS and of its homologs in the blebs mouse mutants[68].

The fused pulmonary lobe 'fpl' mutant rat model

Fused pulmonary lobes (fpl) mutant rats exhibit similar phenotypes to FS[69]. Based on this observation, Kiyozumi et al., have sequenced the DNA of the fpl/fpl mutant mice. They found that the fpl gene harbors a nonsense mutation that introduced a stop codon in FS-associated gene Frem2. Thus, the Fpl mutant was defined as a first rats model of human FS[70].

Zebrafish model

Zebrafish seems to be an ideal genetic model to understand the pathology and the genetic heterogeneity underlying FS[33]. In 2011, Talbot et al., have shown that zebrafish fras1 mutants exhibit defects in facial epithelia and facial skeleton which participated to the comprehension of the developmental basis of facial defects in FS[71]. The potential involvement of several other genes such as Hemicentin1 (HMCN1), Furin, and Fibrillin2 that interact in basement membrane anchorage has been proposed based on the study of zebrafish, suggesting further genetic heterogeneity for FS[72]. Zebrafish have also allowed the identification of novel component of the FC complex (the protein AMACO, an extra cellular matrix protein encoded by the VWA2 gene)[73].

<u>In vitro model</u>

Four human cell lines derived from male FS patients are proposed by the Coriell Institute for Medical Research (New Jersey, United Stated, https://www.coriell.org/OmimNum:219000; Table 4).

Key historical events

The first description of the cryptophtalmos-syndactily syndrome was reported in 2 pairs of siblings by George Fraser in 1962[1]. Several key events have contributed to this description. In 79 AD, Pliny the Elder (Gaius Plinius Secundus) reports in his Book VII of his "*Naturalis Historia*" the observation of a couple having three children born with an eye covered by a skin membrane[11,74]. This is the first report of "hidden eyes" with a family history. In 1872, Zehender and Manz introduced for the first time the term cryptophthalmos ("hidden eye") to describe the case of a six-month old girl[75]. In 1902, Golowin reports the first case of an alive adults with cryptophthalmos and having an affected sister[76]. In 1906 Asayama reported consanguine mice with cryptophthalmos which can be regarded as the first cases of the blebbing mutants in mice[77]. The older literature on cryptophthalmos with associated malformations was reviewed by Duke-Elder in 1963[78].

New historical case of adult FS

Presentation

We report the case of an adult untreated patient with FS from the personal collection of the Surgeon General Gustave Ginestet and never published before. This patient presented some malformations classically described in the syndrome but also some specific maxillofacial characteristics. The patient presented bilateral complete cryptophthalmos, bilateral coloboma of eyelid, bilateral and asymmetric cleft (on the right side the cleft was complete reaching the lip, the maxillary and palate while the cleft was limited to the lip on the left side), short philtrum. Nasal anomalies were a broad nose with midline groove towards the tip, hypoplastic nasal alae and widely set nostrils. The other maxillofacial disorders were facial asymmetry, musculo-skeletal abnormalities (hypoplasia of orbital bones), hypertelorism, a tongue of hair extending from the anterior hairline to the forehead, the eyebrows and the upper-outer edge of the orbit, a short neck, upward slanting palpebral fissures. The dental exam found dental hypoplasia and microdontia (Fig1a, 1b).

Maxillofacial management

This patient was surgically managed by the maxillofacial surgeon General Gustave Ginestet. Thus, he was operated several times (multi-step strategy) for its maxillofacial disorders before the first description of cryptophtalmos-Syndactily syndrome by George Fraser in 1962[1] (Fig1c, 1d and Fig2). Firstly, the patient was operated to repair the bilateral cleft with primary cheiloplasty and rhinoplasty (Fig 1c, 1d). Then, several other rhinoplasties and cheiloplasties were realized (Fig2). Briefly, bilateral local foreheads, orbital flaps were prepared and progressively modified until allowing reconstruction of the nasal base with the two nostrils, the tip and the supra tip. The final result is very interesting (Fig2c, 2d)."

Conclusion

Fraser syndrome (FS) was first described in 2 pairs of siblings by George Fraser in 1962. To date, more than 250 patients have been described in the literature. The clinical variability associated with FS supports the genetic heterogeneity of the syndrome. To our knowledge, there have been only n=3 previously reported cases of a patient fulfilling the diagnostic criteria for FS and surviving over the age of 20 years. Numerous clinical trials and research models are available to better characterize this syndrome in clinical, pathophysiological and genetic terms.

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All authors have viewed and agreed to the submission.

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Figure and table legends

Figure 1. Historical case of an adult patient surgically managed by the maxillofacial surgeon General Gustave Ginestet before the first publications of FS by George Fraser in 1962. 1a and 1b: The patient presented some maxillofacial malformations classically described in the FS: bilateral complete cryptophthalmos, bilateral coloboma of eyelid, the eyebrows and the upper-outer edge of the orbit, upward slanting palpebral fissures, a tongue of hair extending from the anterior hairline to the forehead, facial asymmetry, hypertelorism, bilateral and asymmetric cleft (on the right side the cleft was complete reaching the lip, the maxillary and palate while the cleft was limited to the lip on the left side), short philtrum, a short neck. Nasal anomalies were a broad nose with midline groove towards the tip, hypoplastic nasal alae and widely set nostrils. Dental anomalies were dental hypoplasia and microdontia. All these elements are particularly suggestive of the FS; 1c and 1d: bilateral cleft repair with primary cheiloplasty and rhinoplasty. (FS: Fraser Syndrome)

Figure 2. Multi step surgical strategy realized by the maxillofacial surgeon General Gustave Ginestet to manage an historical case of an adult patient with FS. 2a and 2b: Preparation of bilateral local foreheads, orbital flaps to reconstruct the nasal base with the two nostrils, the tip and the supra tip. 2c and 2d: final results of the surgical management. The aesthetic result is very interesting. (FS: Fraser Syndrome)"

Table 1. Adult cases (age>20 years old) of Fraser Syndrome reported in literature. (NA: non-available)

Table 2. Diagnostic criteria for Fraser syndrome published by Van Haelst et al.,2007.

Table 3. Frequency of the most reported congenital anomalies for published series of patient with Fraser syndrome.

Table 4. Human cell lines derived from male FS patients proposed by the Coriell Institute for Medical Research (New Jersey, United Stated, https://www.coriell.org/OmimNum:219000) (LCL: Lymphoblastoid Cell lines; DNA: deoxyribonucleotidic acid; YR: years; FW: fetal weeks)**.**