Fraser Syndrome - a Case Report and Review of Literature

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**ABSTRACT**

Fraser syndrome is a rare autosomal recessive genetic disorder characterized by major features such as cryptophthalmos, syndactyly, malformations of the larynx and genitourinary tract, craniofacial dysmorphism, orofacial clefting, mental retardation and musculoskeletal anomalies. In total, about 150 affected patients have been described in the literature. The diagnosis of this syndrome can be established after clinical examination. We present the clinical findings of a rare case of Fraser syndrome with lethal phenotype due to bilateral renal agenesis in a female stillborn.

**Keywords**: Fraser syndrome, cryptophthalmos, syndactyly, urogenital malformation

**INTRODUCTION**

Fraser syndrome (also known as cryptophthalmos-syndactyly syndrome, Meyer-Schwickerath’s syndrome, Fraser-François syndrome or Ullrich-Fechtiger syndrome) (1) is a very rare autosomal recessive disorder characterized by major features such as cryptophthalmos, syndactyly, malformations of the larynx and genitourinary tract, craniofacial dysmorphism, mental retardation and musculoskeletal anomalies (2). The syndrome is named after the Canadian genetician George R. Fraser, who first described this disorder in 1962 (3). The incidence of Fraser syndrome is below 0.043 per 10,000 live born infants and 1.1 in 10,000 stillbirths (4), making it a very rare syndrome. Another population-based epidemiological study of 12,886,464 births using data provided by the European Surveillance of Congenital Anomalies (EUROCAT) network of birth defect registries reported a prevalence of 0.2 per 10,000 births (5).

The genetic background of this disease has been linked to FRAS1, a gene involved in skin epithelial morphogenesis during early development (6). The FRAS1 gene is located on the long arm of chromosome 4 (4q21). This disorder has also been associated with FREM2 gene found in chromosome 13 (7) and with GRIP1 mutations of chromosome 12 (8).

The proper diagnosis of Fraser syndrome can be made upon birth based on its distinctive features.
association of malformations. Occasionally, it is possible to diagnose this syndrome due to atypical prenatal ultrasonographic features such as polyhydramnios or oligohydramnios, echogenic lungs and renal abnormalities or agenesis (9).

The treatment and prognosis of Fraser syndrome usually has to deal with the severity of cerebral, pulmonary, laryngeal and renal malformations. Some cases may benefit from proper genetic counseling.

**CASE REPORT**

An autopsy was performed on a female stillborn with multiple congenital malformations to determine the cause of death. The stillborn was the product of the second pregnancy of non-consanguineous healthy parents, delivered by cesarean section. The stillborn weight was 1.480 g and the length was 38 cm.

Gross examination revealed a severe facial dysmorphism with complete bilateral cryptophthalmos, low set ears, flat nasal bridge, micrognathia and incomplete ossification of the skull bones. We noticed complete bilateral syndactyly on both hands and feet. Also, the newborn had an umbilical hernia, imperforate anus and ambiguous genitalia. Major internal organ anomalies were observed: hypoplastic lungs, patent ductus arteriosus and foramen ovale, bilateral renal agenesis with agenesis of the ureters, hypertrophic adrenal glands, hypoplastic bladder. We also noticed two small paraovarian nodules which proved to be ectopic adrenal tissue on histopathological examination.

However, the causes of death were due to an association of acute respiratory insufficiency (caused by massive pulmonary hemorrhage) and bilateral renal agenesis.

**DISCUSSION**

The diagnosis of Fraser syndrome can be made on clinical examination using the diagnostic criteria proposed by Thomas et al (10). The major criteria include cryptophthalmos, syndactyly, sibling with cryptophthalmos and abnormal genitalia. The minor features are congenital malformations of the nose, ear and larynx, skeletal defects, umbilical hernia, renal agenesis and mental retardation. The presence of two major criteria or one major and four minor criteria are needed for diagnosis. In our case all these requirements are satisfied. Before the involvement of genetic mutation was clarified, Thomas et al. highlighted the teratogenic effect of hypovitaminosis A in some animal models such as pigs and rats. Malformations similar to those found in Fraser syndrome are produced when these animals are exposed to a low retinoid diet (10).

The parents of affected children are sometimes, but not always consanguineous. Consan-

![FIGURE 1. Phenotypic features of Fraser syndrome. Note the severe facial dysmorphism with complete bilateral cryptophthalmos, multiple nasal anomalies and micrognathia, congenital umbilical hernia, ambiguous genitalia, complete bilateral syndactyly (Type IV) of the hands and feet, imperforate anus.](image-url)
guinity is reported in 15–24% of cases and the recurrence rate among siblings is about 25% suggesting an autosomal recessive pattern of inheritance (11,12).

Gattuso et al. estimated the frequency of several clinical manifestations of Fraser syndrome based on 3 new cases and by reviewing 68 already published cases. Craniofacial abnormalities were found in all cases, cryptophthalmos in 93%, and syndactyly in 54% (13). They also mentioned Warkany (1971) as citing the description by Pliny the Elder in the first century A.D. of a family with 3 children born with a membrane over the eye, thus suggesting that the major feature of Fraser syndrome was well known since ancient times.

Slavotinek and Tifft reviewed 117 cases of Fraser syndrome or cryptophthalmos published after the comprehensive review of Thomas et al. in 1986. Their findings emphasized the clinical variability associated with this syndrome and highlighted the heterogeneity of the disorder. They also noted syndromic associated anomalies (for example, bicornuate uterus with imperforate anus or anal stenosis and renal malformations) that are found in other syndromes and associations without cryptophthalmos, suggesting that common mutant genes may justify some of the phenotypic variation found in some cases of Fraser syndrome. They conclude by suggesting that categories of physical anomalies or phenotypic features can be preserved across different syndromes and that they may prove to be useful tracks for the delineation of specific abnormalities within a syndrome and for the determination of relevant molecular screening tests (11).

Van Haelst et al. studied the phenotype of 59 newly diagnosed cases with Fraser syndrome from 40 families, including 25 consanguineous families. Compared to previous reviews, they reported a higher frequency of abnormalities of the skull, larynx, umbilicus, urogenital tract and anus, and a lower frequency of mental retardation and cleftoschisis with or without palatoschisis. According to the revised diagnostic criteria proposed by Van Haelst et al., the airway tract and urogenital anomalies should be included as major criteria while mental retardation and clefting should be removed (2).

Prenatal diagnosis of Fraser syndrome is possible as early as 18 weeks into the pregnancy and is accomplished due to the detection via ultrasound and fetoscopy of a combination of syndromic malformations or phenotypic features such as those above-mentioned. Diagnosis of the syndrome should be straightforward when the four cardinal features of cryptophthalmos, abnormalities of the ear and nose, syndactyly and urogenital malformations are present. When cryptophthalmos is the only external abnormality it is important to investigate the patient for underlying urinary or genital abnormalities. Cryptophthalmos without associated malformations is a completely different, freestanding pathological entity and has been reported as an autosomal dominant inheritance pattern.

Treatment options are limited. Therefore, genetic counseling plays an important role. When recommended, surgical treatment may be an appropriate option to correct some of the malformations associated with this disorder.

**CONCLUSION**

The diagnosis of Fraser syndrome can be made on clinical examination and perinatal autopsy and should be taken into consideration in patients with a syndromic combination of acrofacial and urogenital malformations with or without cryptophthalmos. As far as we know this is the first case diagnosed and reported in Romania.
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REFERENCES


