Research Paper Medical Science

Fraser Syndrome in Three Consecutive Siblings : A Case Report

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ABSTRACT

Fraser syndrome is a rare autosomal recessive multisystem disorder characterised by features such as cryptophthalmos, syndactyly, congenital malformations and abnormal genitalia. We report a case and its two elder siblings who had multiple congenital anomalies and clinico radiological features consistent with Fraser syndrome.

KEYWORDS Fraser syndrome , Cryptophthalmos , Syndactyly.

Introduction :

Fraser syndrome (FS: cryptophthalmos syndrome) is a rare inherited disorder characterized by cryptophthalmos, cutaneous syndactyly, craniofacial dysmorphism, orofacial clefting, mental retardation, malformations of the larynx , genitourinary tract and musculoskeletal anomalies.[1] Consanginuity is reported in 15 - 24.8% of the cases. Incidence of Frasers syndrome is 0.043 per 10,000 live born infants and 1.1 in 10,000 stillbirths[2]. C R Fraser, a Canadian geneticist, first described the syndrome in 1962.[3] It has an autosomal recessive inheritance pattern with marked variability of expression. Mutations in the FRAS1 gene or in the FREM2 gene located on the long arm of chromosome 4 (4q21) have been reported to underlie FS, indicating genetic heterogeneity.[4] In medical literature, FS has been reported in siblings.[5,6]

Case Report:

A 2 year old male child, the fifth child of second degree consanguinous healthy parents. Clinical examination at arrival to our hospital at the age of 2 yrs age revealed prominent forehead, absent eyelids and eyebrow over the right eye with eyeball completely covered with skin (complete cryptopthalmos) (Fig.1). The eyeball was palpable underneath. On the left side, the upper eyelid was fused to the cornea and sclera and was devoid of eyelashes (incomplete cryptophthalmos). History of coloboma of left eye, operated on day 20 of life. The lens appeared clear, the pupil was normal and reacted to light in the left side. Blink reflex was present. The child had malformed and bilateral low-set ears (Fig.2), wide and flattened nasal bridge, high arched palate (Fig.3), tongue tie, low set hair line, pseudo-hypertelorism, right sided partial syndactyly, left sided complete syndactyly(Fig.4) and both right and left partial syndactyly between 4th and 5th toes, spine, vertebrae and other systems including cardiovascular system was normal. d Ultrasound of abdomen and pelvis showed absent right kidney(Fig 5).

There was a history of similar anomalies in two previous siblings. The first sibling was a boy, still born, with complete cryptophthalmos of one eye and antenatal ultrasound revealing single kidney. The second sibling was antenatally diagnosed with bilateral renal agenesis at 24 weeks of gestation and was aborted. The aborted fetus also had findings of cryptopthalmos.



Fig.1 Cryptophthalmos



Fig.2 Low set ears



Fig.3 High arched palate



Fig.4 Complete syndactyly



Fig.5 : Empty Right renal fossa



Fig.6 : Normal Left kidney

Discussion :

The earliest reports of what is now known as cryptophthalmos (hidden eye) date back to the first century A.D. Pliny the Elder described the Lepidus family in which three children were born with a membrane over the eye, typical of this rare anomaly.

The findings in our case are compatible with the diagnosis of FS according to the diagnostic criteria proposed by Thomas et al (Table).[7, 8] Two major and one minor criteria or one major

and at least four minor criteria are needed for diagnosis.[7, 8]

Table: Diagnostic criteria of cryptophthalmos syndrome.

Major :	Minor :
• Cryptophthalmos	• Congenital malformation of the nose
• Syndactyly	• Congenital malformation of the ears
• Abnormal genitalia	• Congenital malformation of the larynx
•Sibling with cryptophthalmos syndrome	• Cleft lip and / or palate
	• Skeletal defects
	• Umbilical hernia
	• Renal agenesis
	• Mental retardation

In our case, there were cryptophthalmos, syndactyly, and sibling with cryptophthalmos syndrome as major criteria and malformations of the nose, ears and renal agenesis as minor criteria. Cryptophthalmos is the leading feature of FS and has been described in 84% to 93% of the patients.[7] Cryptophthalmos is a failure of eyelid separation and absence of palpebral fissure mostly with varying absence of eyelashes and eyebrows and defects of the eye, especially the anterior part. It can be unilateral or bilateral, and is classified into three types: complete (the eyelid is completely fused over an existing eye), incomplete (the eyelid is only partially fused over the underlying eye), and abortive (the eyelid is completely fused and the underlying eye does not form). In Frasers syndrome, the defect of eyelid development is frequently accompanied by ocular anomalies; hence, achieving adequate visual perception is poor. Our case had bilateral cryptophthalmos; the right complete and the left incomplete.

Syndactyly has been considered as a major feature of FS that occurs in 77% of the patients. Syndactyly is always cutaneous and, in most cases, involves fingers and toes.[7] Genital anomalies are cryptorchidism, micropenis, phimosis, and hypospadias in male, and clitoromegaly, bicornuate uterus, uterine hypoplasia, vaginal agenesis, and hypoplasia of the labia in female infants. In our case, there was cutaneous syndactyly involving the fingers.

Hair growth pattern may be abnormal. Hearing is usually normal. Consanguinity is reported in 15–24% of cases and the recurrence rate among siblings is 25%.[1] and an autosomal recessive pattern of inheritance. Prenatal diagnosis by means of fetoscopy and antenatal ultrasonography is suggested as early as 18 weeks of gestation, particularly in families with affected siblings.[9] FS should be suspected in all cases of stillbirths with renal agenesis.[10] The type and severity of the renal or laryngeal malformations determines the prognosis and chances of survival. 25% of affected fetuses are stillborn and 25% die during the first few weeks of life and death is usually secondary to renal agenesis and laryngeal stenosis. Therefore, ultrasonography in consanguineous parents, families with a previously affected child, and cases of stillbirths with renal agenesis is recommended. With cryptophthalmos, prognosis with regard to sight is uniformly poor. Prevention by genetic counseling would be the best choice for prevention of recurrence.

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