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RESEARCH ARTICLE

FRASER SYNDROME: CASE REPORT WITH REVIEW OF LITERATURE.

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Abstract

Fraser syndrome is a rare, autosomal recessive multi-system disorder with a reported incidence of 0.043 per 10,000 live born infants and 1.1 in 10,000 stillbirths. The condition is characterized by cryptophthalmos, cutaneous syndactyly, laryngeal and genitourinary malformations, craniofacial dysmorphism, orofacial clefting, musculoskeletal anomalies and mental retardation. The diagnosis can be made on prenatal scans, post natal clinical examination or on autopsy findings. We report a case of an infant who presented with multiple congenital abnormalities and clinical and radiological features suggestive of Fraser syndrome.

Introduction:-

Fraser in 1962 described the four cases of cryptophthalmos and other multiple malformations in two sibsheps[1]. Francois found four cardinal features like cryptophthalmos, syndactyly, malformation of external genitalia and anomalies of nose and ears with less constant features like renal agenesis and laryngeal stenosis[2]. Fraser syndrome (FS) is an autosomal recessive condition with incidence of 0.043 per 10,000 live born infants and 1.1 in 10,000 stillbirths, making it a rare syndrome[3, 4]. Mutations in FRAS1, FREN1, FREM2 and GPIP1 gene have been reported to underlie FS, indicating genetic heterogeneity[5, 6]. These genes encode the extracellular matrix proteins that are necessary for the adhesion between basement membrane of epidermis and connective tissues of dermis during embryological development. The diagnostic criteria are divided in major and minor criteria[7] (Table 1). The diagnosis is confirmed by presence of two major criteria and one minor criteria or one major and at least four minor criteria. Cases with isolated cryptophthalmos which do not have FS have also been reported. We report a case of an infant who presented with multiple congenital abnormalities and clinical and radiological features suggestive of FS.

Case Report:-

A six months old male infant of Indian origin, weighting 4.5kilogram (kg) presented to our plastic surgery outpatient clinic for assessment of coloboma of right eye, cryptophthalmos of left eye and syndactyly. He was the 2nd child of healthy non-consanguineous marriage, delivered by LSCS at 40 weeks of gestation. Birth weight was 2.8 kilogram

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(kg) and length of 44 centimeters (cm). There was no significant drug history during the pregnancy. First baby was a full term normal baby delivered by natural birth. The mother of the baby was 26 years old.

Figure 1a and 1b:- showing coloboma of right upper eye lid (black arrow) and left sided cryptophthalmos

Clinical examination revealed a normal anterior and posterior segment of the right eye with coloboma of the right upper eyelid (figure 1a). Left complete cryptophthalmos was noted with a palpable eyeball beneath (Figure 1b) and nasal deformity. Bilateral testes were absent in the scrotum (figure 1c) and were palpable in the bilateral inguinal canals. Syndactyly of all fingers of bilateral hands (figure 1d) and all toes of bilateral feet were also present. Further ultrasound scan revealed left renal agenesis. Non contrast computerized tomography (NCCT) head and upper face confirmed left cryptophthalmos (Figure 2a and b). A diagnosis of Fraser syndrome was made based on the above clinical and radiological findings. Genetic testing revealed mutation of the FRAM2, which further confirmed the diagnosis of Fraser Syndrome. Patient was planned for surgery - correction of right eye coloboma and left cryptophthalmos in first setting (figure 3a and 3b) followed by correction of syndactyly, nasal deformity and bilateral un descended testes in next settings.

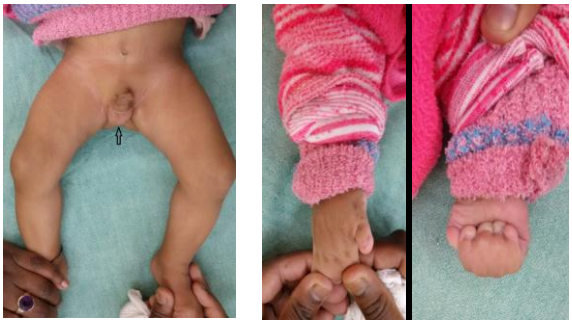

Figure 1c and 1d:- Showing bilateral undescended testes(black arrow) and syndactyly of hands

Discussion:-

Fraser syndrome comprises of cryptophthalmos with defects in urogenital system, eyes, limbs, ears, nose and other organs. It is caused by mutation in FRAS 1 gene located on the long arm of chromosome 4 (4q21), FREM2 gene on chromosome 13, FREN1 and GPIP1. [5,6,12] It is inherited in autosomal recessive fashion. The term cryptophthalmos was introduced by Zehender et al.[10] in 1872 who described a child whose eyes were covered by continuous sheets of skin from forehead to cheek, associated with additional malformations including hypertelorism, syndactyly, abnormal genitalia, umbilical hernia, anal stenosis and hoarse voice. George Fraser[11] in 1962 was the first to group these features together under the term "cryptophthalmos syndrome". In fact, cryptophthalmos is not always a feature of this syndrome, and thus, the eponym Fraser syndrome is preferable for the condition. Thomas et al. in 1986 proposed the diagnostic criteria for FS which included four major and eight minor criteria (table 1). Our patient fulfilled the diagnostic criteria proposed by Thomas et al.[7] which consists of at least two major and one minor or one major and four minor criteria for the diagnosis. Haelst et al.[13] in 2007 proposed a revised diagnostic criteria of FS in which the urogenital and airway tract anomalies were included in the major criteria and clefting and mental retardation were removed from the criteria. The diagnosis can be made if either three major criteria, or two major and two minor criteria, or one major and three minor criteria are present in the patient.

Table no 1:- Diagnostic criteria of Fraser syndrome

Major criteria	Minor criteria
1. Cryptophthalmos	1. Congenital malformation of nose
2. Syndactyly	2. Congenital malformation of ears
3. Abnormal genetalia	3. Congenital malformation of larynx
4. Sibling With Fraser syndrome	4. Clift lip +/- palate
	5. Renal agenesis
	6. Umbilical hernia
	7. Skeletal defects
	8. Mental retardation

The etiopathogenesis of FS is not known exactly. It is believed that it is related to failure of programmed cell death or a defect in metabolism of retinoids.[14] the developmental defects are suggested to arise from disruption of the epithelial-mesenchymal interaction required for normal morphogenetic processes.[15]

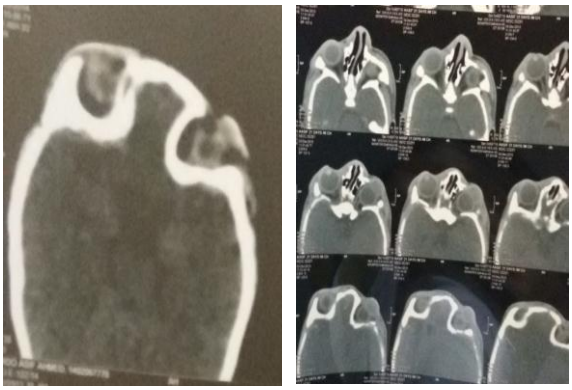

Figure 2a and 2b:- Non contrast computerized tomography of head and upper face showing complete covering of the right eye with skin and soft tissue (cryptophthalmos)

Cryptophthalmos (covered or hidden eye) is defined as failure of separation of eyelids and absence of eyelashes and eyebrows and defects of the eye, mostly anterior chamber[16]. It is classified as complete (the eyelids are fused completely over the existing eye), incomplete (the eyelids are partially fused over the underlying eye) and abortive (the eyelids are completely fused and the underlying eye does not form).[16] It can be unilateral or bilateral. Sometimes but not always the parents are consanguineous. Consanguinity is reported in 15 – 24% of cases and recurrence is about 25% in siblings.[17]There are no reports of molecular genetic studies for prenatal diagnosis of Fraser syndrome. Prenatal diagnosis of Fraser syndrome includes ultrasonography as early as 18 weeks of gestation[8] and fetoscopy.

Figure 3a and 3b:- Showing facial appearance after the initial surgery for left cryptophthalmos and right upper lid coloboma.

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