

Fraser Syndrome: A Rare Case Report

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ABSTRACT

Fraser syndrome is a rare congenital autosomal recessive condition. It is characterized by cryptophthalmos, craniofacial dysmorphism, syndactyly, laryngeal and genitourinary malformations and musculoskeletal anomalies. Here we report a case of a neonate who presented with multiple congenital abnormalities and clinical features that suggest the possibility of Fraser syndrome.

Keywords: Cryptophthalmos; Fraser Syndrome; Neonate; Syndactyly

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INTRODUCTION

Fraser Syndrome is a rare autosomal recessive malformation which is characterized by cryptophthalmos, syndactyly, anomalies of nose and ears, laryngeal and urogenital defects¹. It has an incidence of 0.43 per 100 thousand live born infants and 11.1 in 100 thousand stillbirths, thus making it as one of the rarest syndrome in world.^{2,3} George Fraser first described this syndrome and he coined it as cryptophthalmos syndrome.³ FRAS1, FREN1, FREM2 and GPII1 genes encode the matrix proteins of extracellular compartment that is needed for adhering connective tissues of dermis as well as basement membrane of epidermis during its embryological development.⁴ Mutations in above mentioned genes have been reported to underlie Fraser Syndrome, that indicate genetic heterogeneity.⁵ Here we report a case of neonate with Fraser Syndrome.

CASE REPORT

A term neonate (Figure 1) was born through spontaneous vaginal delivery to a 24 year old female at Karnali Academy of Health Sciences (KAHS), Jumla. Baby's birth weight and length was 1400 gram and 45 cm respectively. Parents belonged to a low socioeconomic background with limited access to medical facilities. No pre-natal record was available. There was no significant drug history during the pregnancy and history of consanguinity. Also, congenital anomalies were not found in the family. After birth baby didn't cry immediately. Apgar score was 3/10 and 4/10 at 1 minute and 5 minutes respectively. Baby was ventilated with bag and mask and then intubated and was transferred to Neonatal Intensive Care Unit (NICU).

Patient party was counseled about the prognosis of baby. On examination, the baby was hypotonic with distended abdomen. Anterior fontanelle was wide open. There was syndactyly of toes of both feet (Figure 2), ambiguous genitalia with a phallus and complete labial fusion (figure 3). The nasal and oral passages were normal. There was prominent occiput, flat nasal bridge,

hypertelorism and dysplastic low set ears. Face bones were malformed. There was single umbilical artery which may suggest genitourinary malformation. Sacral dimpling with tuft of hair and protusion of tail like appendages at back in sacrum likely lipomeningocele were also seen. On cardiovascular examination, pansystolic murmur was ausculted suggesting some congenital cardiac defect. Corneal opacification, absent eyelashes, widely spaced nipples and low hair line were noted. Congenital talipes equinovarus (clubfoot) was also noted on both legs. Remainder of the systemic examination was unremarkable. Baby's chest radiogram seems to be normal. After 3 hours of birth, baby expired. Autopsy was not done due to cultural constraints.



Figure 1: Newborn with multiple anomalies



Figure 2: Syndactyly (Fused toes of both lower limbs)



Figure 3: Ambiguous Genitalia with syndactyly

DISCUSSION

Also known as Fraser-François syndrome or Ullrich-Feichtiger syndrome⁶, Fraser syndrome comprises of cryptophthalmos with anterior segment abnormalities like corneal clouding, sclerocornea, microphthalmia, microcornea and anophthalmia, anomalies of nose, ears, limbs and urogenital system.⁷ Cryptophthalmos is not always a presenting characteristics of this syndrome; so 'Fraser syndrome' is more used or it is preferred than cryptophthalmos syndrome.⁸ Thomas et al. proposed the diagnostic criteria in 1986 that included four major and eight minor criteria for Fraser syndrome.⁹ Van Haelst et al. (Table 1)⁴ recently revised that criteria. By that criteria if three major criteria, or two major and two minor criteria, or one major and three minor criterion are present, diagnosis of Fraser syndrome can be made.¹⁰ In our case, we have syndactyly and abnormal genitalia as two major criteria and dysplastic ears, nasal anomalies and umbilical abnormalities as the minor criterion.

Cryptophthalmos has been described in 84% to 93% of the patients and is one of the primary features of FS. But it isn't always a regular finding in this syndrome. Similarly, syndactyly occurs in almost 77% of the patients.¹¹ Other problems that may be found are congenital malformations of the nose, ear, larynx, genital and umbilical abnormalities, skeletal defects and renal agenesis. Microcephaly, hydrocephalus and encephalocele are some of the occasional neurological abnormalities that we may see in this syndrome.^{7, 12}

Severity of the associated defect will determine the actual prognosis of this syndrome.¹³ It has been found that 25% of affected individuals are stillborn and an additional 20% die before their first birthday.⁷

Diagnosis of Fraser syndrome prenatally includes ultrasonography as early as 18 weeks of gestation as well as fetoscopy.¹⁴ Increased level of maternal serum alpha-fetoprotein (AFP) level may also increase the suspicion of Fraser syndrome.¹⁵

Table 1: Diagnostic criteria of Fraser syndrome⁴

MAJOR CRITERIA	
Syndactyly,	
Cryptophthalmos spectrum	
Ambiguous genitalia	
Urinary tract abnormalities	
Laryngeal and tracheal anomalies	
Positive family history	
MINOR CRITERIA	
Anorectal defects	
Dysplastic ears	
Nasal anomalies	
Skull ossification defects	
Umbilical abnormalities	

CONCLUSION

Fraser syndrome is a rare genetic disease of multiple fetal abnormalities and since ultrasound diagnostic criteria helps in its diagnosis, it is important for physicians and radiologists who perform anomaly screening ultrasound to be familiar with its criteria so that it helps in its timely diagnosis and as well as management. Since Fraser syndrome carries poor prognosis, prenatal diagnosis and genetic counseling is the best approach to prevent this lethal disease.¹⁶

REFERENCES

1. Fraser G. Fraser syndrome: two millennia of cryptophthalmos from Pliny the Elder to FRAS, FREM and GRIP: a historical perspective. *Open J Genet* 2013; 3:1-7. <https://dx.doi.org/10.4236/ojgen.2013.32A3001> [Google Scholar]
2. Azevedo ES, Biondi J, Ramalho LM. Cryptophthalmos in two families from Bahia, Brazil. *J Med Genet* 1973; 10:389-92. <https://dx.doi.org/10.1136/jmg.10.4.389> [Google Scholar] PMID: 4774831
3. Narang M, Kumar M, Shah D. Fraser-cryptophthalmos syndrome with colonic atresia. *Indian J Pediatr* 2008; 75(2):189-91. <https://dx.doi.org/10.1007/s12098-008-0030-9> [Google Scholar] PMID: 18334805
4. Thomas IT, Frias JL, Felix V, Sanchez de Leon L, Hernandez RA, Jones MC. Isolated and syndromic cryptophthalmos. *Am J Med Genet* 1986; 25:85-98 <https://dx.doi.org/10.1002/ajmg.1320250111> [Google Scholar] PMID: 3099574
5. Kiyozumi D, Sugimoto N, Sekiguchi K. Breakdown of the reciprocal stabilization of the QBRICK/Frem1, Fras1 and Frem2 at the basement membrane provokes Fraser syndrome like defects. *Proceedings of the National Academy of Sciences, U S A.* 2006; 103:11981-6 <https://dx.doi.org/10.1073/pnas.0601011103> [Google Scholar] PMID: 16880404

6. Francannet C, Lefrancois P, Dechelotte P, Robert E, Malpuech G, Robert JM. Fraser Syndrome with renal agenesis in two consanguineous Turkish families. *American Journal of Medical Genetics*. 1990;36(4):477-479. <https://dx.doi.org/10.1002/ajmg.1320360421>[Google Scholar] PMID: 2389805
7. Jones KL. *Smith's recognizable patterns of human malformation*, 6th ed. Philadelphia, Elsevier Saunders. 2006; 270- 271.
8. Hoefele J, Wilhelm C, Schiesser, Mack R, Heinrich U, Weber LT, et al. Expanding the mutation spectrum for Fraser syndrome: identification of a novel heterozygous deletion in FRAS1. *Gene* 2013; 520:194-7. <https://dx.doi.org/10.1016/j.gene.2013.02.031>[Google Scholar] PMID: 23473829
9. Thomas IT, Frias JL, Felix V, Sanchez de Leon L, Hernandez RA, Jones MC. Isolated and syndromic cryptophthalmos. *Am J Med Genet* 1986; 25:85-98. <https://dx.doi.org/10.1002/ajmg.1320250111>[Google Scholar] PMID: 3099574
10. Van HM, Scambler PJ, Hennekam RC. Fraser syndrome: a clinical study of 59 cases and evaluation of diagnostic criteria. *Am J Med Genet*. 2007; 143A (24): 3194-203. <https://dx.doi.org/10.1002/ajmg.a.31951>[Google Scholar] PMID: 18000968
11. Slavotinek AM, Tifft CJ. Fraser syndrome and cryptophthalmos: review of the diagnostic criteria and evidence for phenotypic modules in complex malformation syndromes. *J Med Genet*. 2002; 39: 623-33. <https://dx.doi.org/10.1136/jmg.39.9.623>[Google Scholar] PMID: 12205104
12. Mena W, Krassikoff N, Philips JB III. Fused eyelids, airway anomalies, ovarian cysts, and digital abnormalities in siblings: A new autosomal recessive syndrome or a variant of Fraser syndrome? *Am J Med Genet* 1991; 40:377-382. <https://dx.doi.org/10.1002/ajmg.1320400327>[Google Scholar] PMID: 1951446
13. Karaman A, Geckinli B, Aydin H. Fraser syndrome: A new case. *GöztepeTıp Dergisi*.2014; 29(1):60-61. <https://dx.doi.org/10.5222/J.GOZTEPETRH.2014.060>[Google Scholar]
14. Schauer GM, Dunn LK, Godmilow L, Eagle RC Jr, Knisely AS. Prenatal diagnosis of Fraser syndrome at 18.5 weeks gestation, with autopsy findings at 19 weeks. *Am J Med Genet* 1990; 37: 583-591. <https://dx.doi.org/10.1002/ajmg.1320370433>[Google Scholar] PMID: 2175543
15. Touré A, Diomandé IA, Nouraly H. Bilateral cryptophthalmos in Fraser syndrome: case report and review of the literature. *J Fr Ophtalmol* 2015; 38:e97-e100. <https://dx.doi.org/10.1016/j.jfo.2014.09.022>[Google Scholar] PMID: 25890591
16. Adnan Aslam Saleem and SorathNoorani Siddiqui. Fraser syndrome. *J Coll Physicians Surg Pak JCPSP*. 2015;25(2): S124-S126. <https://dx.doi.org/10.2015/JCPSP.S124S126>[Google Scholar] PMID: 26522198