

## Bilateral Cryptophthalmos as the Ocular Manifestation of Fraser Syndrome: A Rare Case Report

Aiman Azhar A.<sup>1,2</sup>, Indriaswati L.<sup>1,2</sup>, Doemilah R.<sup>1,2</sup>, Zuhri N.<sup>1,2,3</sup>

<sup>1</sup>Department of Ophthalmology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

<sup>2</sup>Department of Ophthalmology, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

<sup>3</sup>Department of Ophthalmology, Universitas Airlangga Hospital, Surabaya, Indonesia

[loeky.indriaswati@fk.unair.ac.id](mailto:loeky.indriaswati@fk.unair.ac.id)

---

Cite this paper as: Aiman Azhar A, Indriaswati L, Doemilah R, Zuhri N (2024) Bilateral Cryptophthalmos as the Ocular Manifestation of Fraser Syndrome: A Rare Case Report. *Frontiers in Health Informatics*, 13 (3), 478-485.

---

### Abstract

**Introduction:** Fraser syndrome, also known by several other names, is a rare genetic disorder with a prevalence of less than 0.043 per 10,000 live births. It is characterized by a unique combination of abnormalities, with cryptophthalmos being a prominent diagnostic feature. The genetic basis of the syndrome has been linked to mutations in the *FRAS1* gene and other related genes. Accurate diagnosis can be made at birth, and the severity of associated abnormalities determines the treatment and prognosis. With its rarity and highly variable combination of manifestation and etiologies, this case report is sought to present a rare case of fraser syndrome in a naturally born term infant. **Case illustration:** An infant with several congenital abnormalities was consulted in the neonatal emergency room. At 2235 grammes, the baby is the fifth child born out of five pregnancies. Exam results supporting the diagnosis of Fraser syndrome included severe facial dysmorphism with bilateral abortive cryptophthalmos, bilateral microtia, limbal dermoid, Tessier 8 facial cleft, nasal deformities, polydactyly on both hands, patent ductus arteriosus, and severe hydrocephalus. **Discussion:** Using the diagnostic standards put forth by Thomas et al., a clinical examination can identify Fraser syndrome. Cryptophthalmos, syndactyly, having a sibling with cryptophthalmos, and deformed genitalia are the main requirements. The congenital nose, ear, and laryngeal deformities, skeletal abnormalities, umbilical hernia, renal agenesis, and mental retardation are the minor characteristics. For a diagnosis to be made, either two major criteria or one major and four minor criteria must be present. Abortive cryptophthalmos, polydactyly in both hands, and congenital deformities of the nose and ears were seen in this instance. **Conclusion:** Fraser syndrome does not presently have a treatment. Surgery is only used to repair the deformities brought on by this illness. The severity of the particular defects determines the prognosis in the absence of therapy. Sadly, children with severe abnormalities often die within the first year of their lives.

**Keyword:** Cryptophthalmos, Fraser Syndrome, Polydactyly.

### INTRODUCTION

Major characteristics of Fraser syndrome, an extremely uncommon autosomal recessive illness, include cryptophthalmos, syndactyly, genitourinary tract and larynx deformities, craniofacial dysmorphism, mental impairment, and musculoskeletal abnormalities [1, 2, 3, 4]. It is also known as Meyer-Schwickerath's syndrome, Fraser-François syndrome, or Ullrich-Feichtiger syndrome [5, 6, 7]. The condition bears the name of George R. Fraser, a Canadian geneticist who originally reported this illness in 1962. Fraser syndrome is an extremely rare syndrome with a frequency of less than 0.043 per 10,000 live births and 1.1 per 10,000 stillbirths [8]. A prevalence of 0.2 per 10,000 births was reported in another population-based analysis of 12.886.464 newborns utilising data from the network of birth defect registries known as European Surveillance of Congenital Anomalies (EUROCAT) [9, 10].

This disease's genetic basis has been connected to FRAS1, a gene that has a role in the early development of skin epithelial morphogenesis [11]. On chromosome 4's long arm is where the FRAS1 gene is found (4q21) [12, 13, 14]. Moreover, GRIP1 mutations on chromosome 12 and the FREM2 gene located on chromosome 13 have been linked to this illness [15, 16, 17].

Because of the unique combination of abnormalities associated with Fraser syndrome, an accurate diagnosis may be made of the condition at birth. Atypical prenatal ultrasonographic characteristics, such as polyhydramnios or oligohydramnios, echogenic lungs, and renal abnormalities or agenesis, can occasionally be used to diagnosis this condition [18, 19, 20]. The severity of the cerebral, laryngeal, pulmonary, and renal abnormalities largely determines the course of treatment and prognosis for patients with Fraser syndrome. Genetic counselling may be beneficial in certain instances. With its rarity and highly variable combination of manifestation and etiologies, this case report is sought to present a rare case of frase syndrome in a naturally born term infant in order to widen the knowledge regarding this disease in order to further expand the research in this topic with a hope that the prevention and management of this disease can be improved in the future.

### CASE REPORT

Our patient, who was consulted at the maternity division emergency room with the primary complaint of malformed eye lids and a mass in the eyes, is a one-day-old newborn with various congenital malformations. This is a rare instance of Fraser syndrome. Disturbances in the fingers, ears, and palate are also observed in conjunction with complaints. History of birth: infant was born naturally between 37 and 38 weeks at term. History of pregnancy: the mother did not use drugs or herbal remedies during her pregnancy, and there were no anomalies or traumatic experiences.



**Figure 1.** Bilateral cryophthalmos (red arrow), bilateral dermoid limbal (black arrow), abnormal tongue of hair (green arrow)

From the current illness's history, the patient was the fifth of five siblings; the third, who had cyanosis and stopped wailing at birth, passed away. There was no family history of the same complaint. Previous medical history: the patient's mother was denied treatment for hypertension and had diabetes for nine years.



**Figure 2.** Facial cleft tessier 8 (black arrow).

During the ophthalmological assessment, both eyes' visual acuity was light responsiveness. Because neither eye has an eyelid, it is challenging to assess intraocular pressure. Bilateral dermoid limbal in both lateral eyelids and bilateral cryptophthalmos in the anterior region were discovered (**figure 1**). In both eyes, the cornea was blurry, making it impossible to assess other details. Upon physical inspection, bilateral digital abnormalities were discovered, along with syndactyly in both hands' (**figure 3**). Bilateral congenital ear deformity was discovered, and anomalies related to the tongue and the high arched palate were discovered in the facial region and later determined to be a facial cleft tessier 8 (**figure 2**).



**Figure 3.** Bilateral polydactyl.



**Figure 4.** Bilateral auricular microtia

A truncus arteriosus with patent ductus arteriosus was diagnosed by the cardiologist; a suspected right and left facial cleft Tessier eight (**figure 2**) with microtia grade four in both ears (**figure 3**) and polydactyly in both hands was noted (**figure 4**); closed fontanelle and sutura were evaluated along with the patient's brain growth and surgery planning at one year old; microcephali with severe hydrocephalus was diagnosed by neurosurgery; no specific therapy was recommended. After the examination, the patient was found to have Fraser syndrome. The patient received artificial tears eyedrop minidoses of one drop every hour in both eyes and antibiotic eye ointment every six hours on both eyes. Unfortunately, the patient died on the age of three weeks with a determined cause of systemic complication notably respiratory distress.

## DISCUSSION

While cryptophthalmos is a prominent diagnostic abnormality in Fraser syndrome, it should not be assumed that the existence of cryptophthalmos inherently indicates the presence of Fraser syndrome, as it does not appear in a single manifestation. This means that, even in cases where other symptoms are present, a patient lacking cryptophthalmos should not be diagnosed with Fraser syndrome [21].

Cryptophthalmos patients would have an abnormal cornea because the developing lid folds interfere with the formation of the cornea. Furthermore, the maxillary and frontonasal processes do not develop into the eyelid folds later on. That complete lack of surface ectoderm growth, or total cryptophthalmos, is therefore incompatible with normal underlying ocular structures makes sense. The parents (and the patient, if the patient is an adult) must be informed of this before surgery is conducted.

Since both syndactyly and cryptophthalmos are believed to be the result of aberrant interactions between the underlying mesenchyme and epithelia, there may be some insight into the development of Fraser syndrome from these links. More recently, it was discovered that a mutation in the FRAS 1 gene on chromosome 4 causes 50% of all people with Fraser syndrome. [21]. This particular region codes for a trans-membrane extra-cellular matrix protein that is important in the formation of the intrauterine epithelium. Fraser syndrome has been associated with other point mutations, including the FRAS 1-related extracellular matrix gene or shortened with FREM 1 which resided on the chromosome 9, due to the disease's variable clinical manifestation [22, 23]. The majority of the FREM 1 product is generated on the dermal rather than the epidermal side of developing epithelia, despite the idea that the FRAS 1 gene product controls multiple embryologic growth factors [9]. FREM 1 is necessary for normal epidermal adhesion throughout development. Although the precise mechanisms underlying the development of eyelid folds at the level of the epithelium and underlying mesoderm are not fully understood, aberrant production of the FREM 1 and FRAS 1 genes in this syndrome is likely to have an influence on the development of eyelid folds at the epidermal/mesenchymal interface.

Thomas et al. in 1986 published the diagnostic criteria for Fraser syndrome for the first time. In 2007, after

looking at 59 cases of Fraser Syndrome, Van Haelst and the Fraser Syndrome Collaboration Group removed mental retardation and clefts from the list of essential criteria, but they added urogenital anomalies and the airway tract. The clinical significance of these traits was also validated. Taking everything into account, two major and one minor criterion or one major and four minor criteria can be used to diagnose Fraser syndrome [24].

- **Major:** right cryptophthalmia with eyeball remodeled in its entirety, without lens, giving the appearance of a colobomatous cyst, total absence of eyebrow and eyelashes, bilateral syndactyly.
- **Minor:** wide nose and depressed nose ridge.

The anomalies that are most commonly documented in the literature are genital abnormalities, unilateral or bilateral cryptophthalmos, renal agenesis, and syndactyly. In addition to cryptophthalmos, other findings related to the maxillofacial and oro-dental domains have been documented [25]. These include facial asymmetry, upward-slanting palpebral fissures, hypertelorism, cleft lip and palate (11%), high arched palate (12%), short neck, supragingival calculus, microdontia, retained deciduous teeth, hypodontia, bilateral coloboma of the eyelid, broad nose and/or nasal bridge (8–84%), malocclusion, dental crowding, fusion of the primary teeth, dental hypoplasia, and short roots [26, 27, 28, 29]. Affected airways (laryngeal compromise) account for 21–83% of cases of FS. The most common laryngotracheal abnormalities are subglottic stenosis and laryngeal webs, often known as laryngotracheal atresia [30].

Other rare ear, nose, and throat abnormalities include malformed and/or low set ears, meatal stenosis or dysplastic pinna, hypoplastic notched nares, and choanal stenosis or atresia. Rare are heart problems and musculoskeletal disorders (Barisic, et al., 2014; Alsaman, Agha, Sallah, Badawi, & Kitaz, 2020; Tessier, et al., 2016; Mangla, et al., 2024). In addition to syndactyly, other musculoskeletal anomalies linked to Fraser Syndrome include genu valgum, bilateral hip dysplasia, diastasis of the pubic symphysis, and skull ossification deficiencies [35]. In people with Fraser Syndrome, syndromic congenital nasolacrimal duct blockages are uncommon [36]. To check for dacryocystoceles, a nasal endoscopic endonasal examination should be done. If required, drainage and marsupialization should also be carried out.

Surgical reconstruction and visual rehabilitation present challenges when dealing with cryptophthalmos, particularly with regard to the eyelid defect [37]. A set of 13 eyeballs from seven Fraser Syndrome patients were disclosed by Saleh et al. in 2009 in an attempt to optimise these individuals' visual potential [38]. The cryptophthalmos was complete in three eyes and abortive in ten. They concluded that while designing the periocular surgical therapy for these complex cases, a systematic approach should be taken. The surgical treatments that should be performed include dissection of corneal adhesions from keratinised cornea, a mucous membrane graft, a Mustardé eyelid switch flap with a division later on, and extra lower lid augmentation as necessary. [39].

## CONCLUSION

In 1962, George Fraser initially reported two sets of siblings who had Fraser syndrome. In the literature, more than 250 patients have been described thus far. The genetic heterogeneity of the disease is supported by the clinical variability linked to Fraser Syndrome. It seems that just three cases have been documented in the past where a patient met the diagnostic requirements for Fraser Syndrome and lived to be older than 20. This highlights the need of good prenatal and postnatal care for pregnant women in our low-resource situation. To provide a more comprehensive clinical, pathophysiological, and genetic description of this illness, a plethora of study models and clinical studies are available. In addition, it is imperative that health professionals—especially obstetricians, midwives, and pediatricians—organize refresher courses on the identification of congenital malformation syndromes at birth. Only then will these potentially fatal genetic disorders be identified in a timely manner and referred to paediatric surgery departments for prompt treatment. Fraser syndrome consequences can be deadly and life-threatening.

**References**

- [1] J. Bouaoud, M. Olivetto, S. Testelin, S. Dakpe, J. Bettoni and B. Devauchelle. (2020). "Fraser syndrome: review of the literature illustrated by a historical adult case," *International Journal of Oral and Maxillofacial Surgery*, vol. 49, no. 10, pp. 1245-1253.
- [2] K. Kalaniti and V. Sandhya. (2011). "Fraser syndrome in three consecutive siblings," *Oman Journal of Ophthalmology*, vol. 4, no. 2, pp. 87-89.
- [3] S. Ikeda, C. Akamatsu, A. Ijuin, A. Nagashima, M. Sasaki, A. Mochizuki, H. Nagase, Y. Enomoto, Y. Kuroda, K. Kurosawa and H. Ishikawa. (2020). "Prenatal diagnosis of Fraser syndrome caused by novel variants of *FREM2*," *Human Genome Variation*, vol. 7, no. 32.
- [4] J. Gattuso, M. A. Patton and M. Baraitser. (1987). "The clinical spectrum of the Fraser syndrome: report of three new cases and review," *Journal of Medical Genetics*, vol. 24, pp. 549-555.
- [5] C. Francannet, P. Lefrancois, P. Dechelotte, E. Robert, G. Malpuech and J. M. Robert. (1990). "Fraser syndrome with renal agenesis in two consanguineous Turkish families," *American Journal of Medicine and Genetics*, vol. 36, no. 4, pp. 477-479.
- [6] M. Thomsen, U. Schneider, M. Weber and F. U. Niethard. (1998). "The different appearance of the oculodentodigital dysplasia syndrome," *Journal of Pediatric Orthopaedics B*, vol. 7, no. 1, pp. 23-26.
- [7] A. Mbonda, F. T. Endomba, U. S. Kanmounye, J. R. Nkeck and J. N. Tochie. (2019). "Diagnosis of Fraser syndrome missed out until the age of six months old in a low-resource setting: a case report," *BMC pediatrics*, vol. 19, p. 292.
- [8] M. Narang, M. Kumar and D. Shah. (2008). "Fraser-cryptophthalmos syndrome with colonic atresia," *Indian Journal of Pediatrics*, vol. 75, no. 2, pp. 189-191.
- [9] I. Barisic, L. Odak, M. Loane, E. Garne, D. Wellesley, E. Calzolari, H. Dolk, M.-C. Addor and L. Arriola. (2013). "Fraser syndrome: epidemiological study in a European population," *American Journal of Medicine and Genetics*, vol. 161A, no. 5, pp. 1012-1018.
- [10] A. Slavotinek and C. Tifft. (2002). "Fraser syndrome and cryptophthalmos: review of the diagnostic criteria and evidence for phenotypic modules in complex malformation syndromes," *Journal of Medical Genetics*, vol. 39, no. 9, pp. 623-633.
- [11] L. McGregor, V. Makela, S. M. Darling, S. Vrontou, G. Chalepakis, C. Roberts, N. Smart, P. Rutland, N. Prescott and J. Hopkins. (2003). "Fraser syndrome and mouse blebbed phenotype caused by mutations in *FRAS1/Fras1* encoding a putative extracellular matrix protein," *National genetics*, vol. 34, no. 2, pp. 203-208.
- [12] S. O. Sag, O. Gorukmez, O. Gorukmez, M. Ture, S. Sahinturk, A. Topak, T. Gulden, D. Schanze, T. Yakut and M. Zenker. (2015). "A novel mutation in the *FRAS1* gene in a patient with Fraser syndrome," *Genetic Counseling*, vol. 26, no. 1, pp. 21-27.
- [13] J. Hoefele, C. Wilhelm, M. Schiesser, R. Mack, U. Heinrich, L. T. Weber, S. Biskup, C. D. Haas, H. G. Klein and I. Rost, "Expanding the mutation spectrum for Fraser syndrome: identification of a novel heterozygous deletion in *FRAS1*," *Gene*, vol. 520, no. 2, pp. 194-197, 2013.
- [14] M. J. Vogel, P. v. Zon, L. Brueton, M. Gijzen, M. C. van Tuil, P. Cox, D. Schanze and A. Kariminejad. (2012). "Mutations in *GRIPI* cause Fraser syndrome," *Journal of Medical Genetics*, vol. 49, no. 5, pp. 303-306.
- [15] D. Schanze, H. Kayserili, B. N. Satkin, U. Altunoglu and M. Zenker. (2014). "Fraser syndrome due to mutations in *GRIPI*--clinical phenotype in two families and expansion of the mutation spectrum," *American Journal of Medicine and Genetics*, vol. 164A, no. 3, pp. 837-840.

- [16] S. Jadeja, I. Smyth, J. E. Pitera, M. S. Taylor, M. v. Haelst, E. Bentley, L. McGregor and J. Hopkins. (2005). "Identification of a new gene mutated in Fraser syndrome and mouse myelencephalic blebs," *National Genetics*, vol. 37, no. 5, pp. 520-525.
- [17] G. T. Turgut, T. S. Sivrikoz, E. K. Bayrak and T. Kalayci. (2023). "FREM2-related Fraser syndrome with popliteal pterygium and structural central nervous system anomalies," *European Journal of Medical Genetics*, vol. 66, no. 3.
- [18] C. Berg, A. Geipel, U. Germer, A. Petersen-Hansen, M. Koch-Dorfler and U. Gembruch. (2001). "Prenatal detection of Fraser syndrome without cryptophthalmos: case report and review of the literature," *Ultrasound Obstetrics and Gynecology*, vol. 18, no. 1, pp. 76-80.
- [19] J. Gattuso, M. A. Patton and M. Baraitser. (1987). "The clinical spectrum of the Fraser syndrome: report of three new cases and review.," *Journal of Medical Genetics*, vol. 24, no. 9, pp. 549-555.
- [20] D. Das, S. Modaboyina, S. Raj, S. Agrawal and M. S. Bajaj. (2022). "Clinical features and orbital anomalies in Fraser syndrome and a review of management options," *Indian Journal of Ophthalmology*, vol. 70, no. 7, p. 2559-2563.
- [21] I. Smyth and P. Scambler. (2005). "The genetics of Fraser syndrome and the blebs mouse mutants," *Human Molecular and Genetics*, vol. 15, no. 14, pp. 69-74.
- [22] D. Kiyozumi, N. Sugimoto and K. Sekiguchi. (2006) "Breakdown of the reciprocal stabilization of QBRICK/Frem1, Fras1, and Frem2 at the basement membrane provokes Fraser syndrome-like defects," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, no. 32, pp. 11981-11986.
- [23] P. Petrou, A. K. Makrygiannis and G. Chalepakis. (2008) "The Fras1/Frem family of extracellular matrix proteins: structure, function, and association with Fraser syndrome and the mouse bleb phenotype," *Connective Tissue Research*, vol. 49, no. 3, pp. 277-282.
- [24] M. M. van Haelst, P. J. Scambler and R. C. Hennekam. (2007). "Fraser syndrome: a clinical study of 59 cases and evaluation of diagnostic criteria," *American Journal of Medicine and Genetics*, vol. 143A, no. 24, pp. 3194-3203.
- [25] G. De Bernardo, M. Giordano, A. Di Toro, D. Sordino and D. De Brasi. (2015) "Prenatal diagnosis of Fraser syndrome: a matter of life or death?," *Italian Journal of Pediatrics*, vol. 41, p. 86.
- [26] A. M. Slavotinek and C. J. Tiffit. (2002). "Fraser syndrome and cryptophthalmos: review of the diagnostic criteria and evidence for phenotypic modules in complex malformation syndromes," *Journal of Medical Genetics*, vol. 39, no. 9, pp. 623-633.
- [27] E. J. Keene and P. F. Day. (2011). "Case report: hypodontia and short roots in a child with Fraser syndrome," *European Archives of Paediatric Dentistry*, vol. 12, no. 4, pp. 216-218.
- [28] Y. Hassona, H. Kharoub and C. Scully. (2017). "Oral healthcare in Fraser syndrome," *Special Care Dentistry*, vol. 37, no. 5, pp. 263-266.
- [29] M. Gallottini, A. H. Llanos, G. A. Romito, M. M. Romano and F. B. de Oliveira. (2018). "Oral manifestations and rehabilitation in Fraser syndrome: A case report," *Special Care Dentistry*, vol. 38, no. 4, pp. 249-254.
- [30] G. R. Ford, R. M. Irving, N. S. Jones and C. M. Bailey. (1992). "ENT manifestations of Fraser syndrome," *Journal of Laryngology and Otology*, vol. 106, no. 1, pp. 1-4.
- [31] I. Barisic, L. Boban, R. Greenless, E. Garne, D. Wellesley, E. Cazolari, M.-C. Addor, L. Arriola, J. E. Bergman and P. Braz. (2014). "Holt Oram syndrome: a registry-based study in Europe," *Orphanet Journal of*

Rare Disease, vol. 9, p. 156.

[32] M. Z. B. Alsaman, S. Agha, H. Sallah, R. Badawi and M. N. Kitaz. (2020). "Bilateral anophthalmia and intrahepatic biliary atresia, two unusual components of Fraser syndrome: a case report," *BMC Pregnancy and Childbirth*, vol. 20, no. 1, p. 358.

[33] A. Tessier, M. Sarreau, F. Pelluard, G. Andre, S. Blesson, M. Bucourt, P. Dechelotte, L. Faivre and T. Frebourg. (2016). "Fraser syndrome: features suggestive of prenatal diagnosis in a review of 38 cases," *Prenatal Diagnosis*, vol. 36, no. 13, pp. 1270-1275.

[34] M. Mangla, A. Kaliappan, A. Srirambhatla, M. Chandrupatla, R. Motwani and N. Kumar. (2024). "Fraser syndrome with limb reduction defect: a rare and unique anatomic variation," *Surgical Radiology and Anatomy*, vol. 46, no. 4, pp. 501-506.

[35] J. A. Soto and C. T. Price. (2008). "The presence of bilateral hip dysplasia and genu valgum in Fraser syndrome," *Orthopedics*, vol. 31, no. 1, p. 81.

[36] S. H. T. Lorena, E. D. Goncalves and M. A. C. Machado. (2014). "Fraser Syndrome: case report in lacrimal system," *Review Brasilia Oftalmologica*, vol. 73, no. 2, pp. 123-125.

[37] T. J. Sullivan, M. P. Clarke and D. S. Rootman. (1992). "Eyelid and fornix reconstruction in bilateral abortive cryptophthalmos (Fraser syndrome)," *Australia and New Zealand Journal of Ophthalmology*, vol. 20, no. 1, pp. 51-56.

[38] G. M. Saleh, B. Hussain, D. H. Verity and J. R. Collin. (2009). "A surgical strategy for the correction of Fraser syndrome cryptophthalmos," *Ophthalmology*, vol. 116, no. 8, pp. 1707-1712.

[39] S. Lessa, M. Nanci, R. Sebastia and E. Flores. (2011). "Two-stage reconstruction for eyelid deformities in partial cryptophthalmos," *Ophthalmic and Plastic Reconstructive Surgery*, vol. 27, no. 4, pp. 282-286.

[40] I. Smyth, X. Du, M. S. Taylor, M. J. Justice, B. Beutler and I. J. Jackson. (2004). "The extracellular matrix gene *Frem1* is essential for the normal adhesion of the embryonic epidermis," *Proceedings of National Academy of Science USA*, vol. 101, no. 37, pp. 13560-13655.