Case report: Fraser syndrome. A stepwise management approach in a very rare condition

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Abstract

Fraser syndrome is a rare genetic disorder inherited in an autosomal recessive manner. This disorder's prevalence is estimated at around 0.20 per 100,000 births in Europe, according to the European Surveillance of Congenital Anomalies (EUROCAT). Here, we reported a bilateral cryptophthalmos case in a four-month-old infant with complete unilateral cleft lip and palate and other syndromic features. We have planned a meticulously staged operation. The first step is cheilonasoraphy, which treats nasal deformity. The hope is to improve the patient's nutritional intake to support the next stage of the operation. Fraser syndrome is a rare medical condition that can make diagnosing and collecting data on missed cases difficult. It's important to consider other diagnostic criteria carefully to avoid confusing the condition with other congenital malformations.

Staged management is a viable option for improving a patient's physiological condition to aid the healing process and support the next stage of the operation.

Keyword: Fraser Syndrome, Cryptophthalmos, chielonasoraphy.

1. Introduction

Cryptopthalmos or Fraser syndrome (FS) was a rare autosomal recessive genetic disorder, first widely introduced by George R. Fraser in 1962. This syndrome has characteristics such as cryptophthalmos, cutaneous

syndactyly, and laryngeal and urogenital anomalies. In addition, several congenital abnormalities such as craniofacial, anorectal skeletal, and heart disorders are often also found to accompany this disorder.

Based on a survey conducted by EUROCAT from January 1990 to December 2008, 0.20 incidents per 100,000 or 1: 495,633 births in Europe were found. It is suspected that this congenital disorder is closely related to mutations in the FRAS1, FREM2, and GRIPI1 genes in the formation of morphogenesis of the skin epithelium in the embryogenesis phase. In addition, in 1986, a study by Thomas et al. found another cause, namely the relationship between the teratogenic effects of vitamin A deficiency and the prevalence of Fraser syndrome. However, of course, this discovery still needs further study.

In 1989, Thomas et al. formulated the diagnostic criteria that are now widely used as a basis for establishing a diagnosis. He grouped these patients into major and minor criteria for establishing a diagnosis of Cryptophthalmos syndrome (Fraser syndrome) and distinguishing it from isolated Cryptophthalmos and other multiple congenital malformations.

In this article, we report the stepwise management of a patient with multiple congenital disabilities, Fraser Syndrome, with cryptopthalmos as the main feature. This case is very rare, and few articles have been published about this syndrome in Indonesia.

2. Case Illustration

A 4-month-16-day-old infant patient came to the plastic surgery clinic of Wahidin Sudirohusodo Hospital with congenital disabilities in the eye area and cleft lip and palate. On examination, it was found that the eyelids were not formed in the left and right eyes, with a complete cleft lip and palate on the right side. It is known that the patient was born spontaneously with a birth weight of ± 3.2 kg, full term. The patient never underwent an ultrasound or other radiology examination during pregnancy. A history of the same disease in the family was denied. The patient came from a poor family, so it was difficult to obtain good health facilities. On further examination, it was found that there was a heart defect, BESSI (benign enlargement of subarachnoid space in infancy), ultrabrachycephalic, Phthisis bulbi, and aphakia oculi dextra. The patient was diagnosed with

Fraser syndrome and was planned to undergo reconstructive management in stages, starting with reconstruction of the lips and nose palate and then making the eyelids. In the initial management stage, we use the Millard technique to perform cheilorraphy and correct the nose (nasorraphy) through the Rethi incision.

Fig 1. Milard Modification Technique

The design of the operation is done by marking points A, B, C, D, E, F, G, P and O using gentian violet as shown in Figure 1. The procedure is done under deep sedation. The incision is made as deep as the skin using a 15 knife and then continued until it reaches the entire thickness of the lip using an 11 knife. The procedure is done from the medial to the lateral side. To form the vermilion and add volume, the lateral vermillion muscle is excised from the skin and then used as a flap. Then, the mucosa in the medial segment is cut 0.5-1 cm above and parallel to the curve of the alveolar mucosa. The tissue above the alveolar mucosa and the periosteum are released to the inside of the nose so that the lip area can be easily moved. An assessment is carried out to adjust the design and incision. On the lateral segment, an incision is made into the nose to the point where it meets the bone. The skin on the lateral vermilion flap is excised. The oral mucosa is cut 1 cm above the lip/gum, and the muscle is released from the periosteum to facilitate the orbicularis oris muscle to be moved medially. A re-assessment is carried out before the suturing stage. The suture is done in stages, layer by layer, according to the

design that has been formed. To correct the nasal deformity, repositioning is done using the Djohansjah technique by making a Rethi incision from the columella to the alanation side. The skin is freed until the alanation cartilage is visible. Repositioning is done on the deformed side of the cartilage and fixed to the other side using polypropylene 6.0 so that the cartilage is parallel and the same height. Excess skin is excised and then the skin is sutured using nylon 6.0. The surgical wound is cleaned and smeared with 1% gentamicin antibiotics and oral antibiotics for 3 days. The wound is cleaned 2-3 times a day with 0.9% NaCl, and the application of antibiotics is. The stitches are removed on the 6th day under general anesthesia.

Fig 2. One-week after surgery

Seven days after the operation, there was no dehiscence, and the flap was viable; the stitches were removed, the wound had closed, the swelling was minimal, and there were no signs of inflammation. The

healing process was as expected, there was no more swelling, and the incision looked pale.

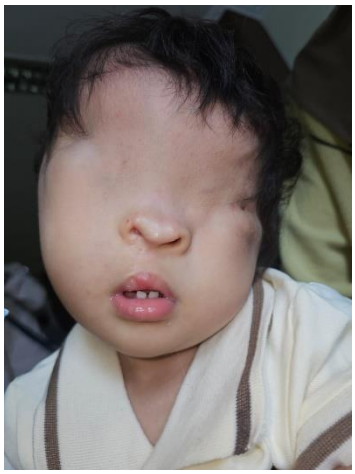

Fig 3. Six-months after surgery

3. Discussion

In this case, it was concluded that the patient suffered from Fraser syndrome, considering that he met the criteria of Thomas et al. 1989 with 1 major cryptophthalmos and four minor ones, namely congenital malformations of the nose, ears, cleft lip, and palate, plus the possibility of mental retardation which can only be examined when the patient is older, in addition to further examination, a heart defect was also found, which was also found in other studies with Fraser syndrome.

The pathophysiology of this case occurs at the age of eight weeks, where eyelid development occurs by periderm cells and fusion of the eyelids. Still, in patients with cryptophthalmos, this does not occur.
Some other scientific sources say that cryptophthalmos is related to mutations in the FRAS 1, FREM 2, and GR1P1 genes, which function to control the production of proteins needed in the adhesion process between the epidermis basement membrane and the dermis connective tissue during embryonic development. Mutations in these genes prevent the development of the eyelids which causes failure of eyelid formation. This also results in the failure of "programmed cell necrosis" in the attachment of the epidermis, causing the formation of large blisters during embryological development.

In establishing a diagnosis of Fraser syndrome based on Thomas et al.'s criteria, at least two major criteria and one minor criterion, or one major criterion and four minor criteria, are required.

Table 1. Fraser syndrome criteria based on Thomas et al's criteria

Diagnostic criteria	
Major criteria	Minor criteria
Cryptophthalmos	Congenital malformation of nose
Syndactyly	Congenital malformation of ears
Abnormal genitalia	Congenital malformation of larynx
Sib with cryptophthalmos syndrome	Cleft lip and/or palate
	Skeletal Defect
	Umbilical Hernia
	Renal Agenesis
	Mental Retardation

These criteria are widely used in establishing cases of Fraser syndrome.

In the study by Slavotinek and Tiff (2002), it was found that cryptophthalmos is an important sign in establishing the diagnosis of Fraser syndrome, so a diagnosis of the syndrome without cryptophthalmos can be considered overdiagnosis. This is because Fraser syndrome itself has a complex and pleiotropic phenotype, leading to a high tendency for overlap with multiple other congenital malformations. In another recent study, Van Haelst et al. (2007) added malformations of the respiratory and genitourinary tracts as major criteria and revised several other criteria as outlined below.

Table 2. Fraser syndrome criteria based on Van Haelst et al's criteria

Major criteria	Minor criteria
1. Syndactyly 2. Cryptophthalmos spectrum 3. Urinary tracts abnormalities 4. Ambiguous genitalia 5. Laryngeal and tracheal abnormalities 6. Positive family history	1. Anorectal defect 2. Dysplastic ears 3. Skull ossification defects 4. Umbilical Abnormalities 5. Nasal Abnormalities

As of the time this article was written, we have not yet found any research comparing those two criteria.

In this case, the author plans to carry out the treatment gradually. It is divided into cheilonasoraphy surgery in the initial stage, followed by palatoplasty, and then eyelid formation surgery.

Fraser syndrome itself is a collection of symptoms, one of which is cryptophthalmos. Since it is a symptom, it is generally accompanied by other symptoms, such as syndactyly. This is caused by the failure of periderm cell development in the eighth week of pregnancy, but in this case, the patient does not have syndactyly on either the hands or feet.

Ambiguous genitalia can also be found in patients with Fraser syndrome; in males, typical findings include cryptorchidism, micropenis, hypospadias, phimosis, and scrotal hypoplasia. Additionally, gastrointestinal abnormalities may appear, such as anal atresia, although anal stenosis and umbilical hernia are rarely observed. In this case, none of the abnormalities mentioned were found.

Death in cases of Fraser syndrome is often caused by renal agenesis or laryngeal stenosis. About 25% die shortly after birth, and another 25% die due to renal agenesis and laryngeal stenosis. Additionally, 80% of Fraser syndrome cases experience mental retardation. In this case, it is not yet known whether the patient has mental retardation or not, and further examination is needed.

Prenatal diagnosis of Fraser syndrome can already be performed at 18 weeks of gestation; this is especially necessary in pregnancies with a family history of CO or FS. On ultrasound, a combination of cryptophthalmos/microphthalmia, syndactyly, enlarged echogenic lungs, and oligohydramnios is usually found.

The existing diagnostic criteria for Fraser syndrome cannot be used for prenatal diagnosis; for example, in cases of oligohydramnios, the appearance of syndactyly or abnormal genitalia is challenging to observe. Therefore, renal agenesis is the most critical factor to examine in prenatal ultrasound. However, in this case, the patient's parents did not have ultrasound examinations during the pregnancy, so prenatal diagnosis could not be performed.

4. Conclussion

Fraser syndrome presents a wide spectrum and combination of congenital defect abnormalities in a minimal number of cases. In these cases, a staged surgical approach is preferred (the benefit of staging) by considering the patient's age and basal metabolic rate undergoing surgery and minimizing the risk of postoperative complications compared to performing all procedures at once.

The first stage in this case produced satisfying results, both functionally and aesthetically. However, as of the time this article was written, the patient has not yet met the criteria for further surgery.

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