A Rare Case of Complete Cryptophthalmos and Suspected Fraser's Syndrome in a Female Neonate

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ABSTRACT: Cryptophthalmos is a rare congenital eye anomaly characterized by the absence of the palpebral fissure. Cryptophthalmos is often associated with Fraser's syndrome. We present a case of 3 days old female Asian neonate with complete unilateral cryptophthalmos, with the absence of a right eyelid. On inspection, there is an absence of eyelid, eyebrow and eyelashes in the right eye, collectively known as adnexal structures. The left eye was apparently normal. As per the parent's decision, surgical intervention was not pursued due to the poor visual prognosis. We advised prenatal genetic screening and testing for future pregnancies. These findings suggest the importance of genetic counseling and testing in cases of cryptophthalmos to identify potential genetic mutations and facilitate appropriate management.

KEYWORDS: Cryptophthalmos, Fraser's syndrome, eyelid, genetic test, case report

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Introduction

Cryptophthalmos is a rare congenital presentation of the eye in which the palpebral fissure is absent. Cryptophthalmos was first described in 1872 and there was absence of the palpebral fissure and continuation of skin from forehead to cheek. The eye was malformed, especially the anterior segment and the eyelids were absent.[1] Autosomal recessive and autosomal dominant modes of inheritance have been reported, but many cases occur sporadically. Cryptophthalmos is commonly seen with Fraser's syndrome.[1,2] Fraser's syndrome is characterized by cryptophthalmos, malformations of the genitourinary tract, the larynx, cutaneous syndactyly, craniofacial dysmorphism, orofacial clefting, mental retardation, and musculoskeletal abnormalities.[3-5] Cryptophthalmos has an equal incidence rate in males and females, with a 1:1 ratio.[1] Cryptophthalmos can occur as either a unilateral or bilateral condition. In some rare cases, it is associated with ambiguous genitalia and anophthalmia or microphthalmia.

Case Report

A 3 days old female Asian neonate brought by her mother presented with a chief complaint of the absence of an eyelid in the right eye. She was born to a 23-year-old primigravida mother through institutionalized c-section delivery. No History of consanguineous marriage. The obstetric history was bad, and the mother reported mild oligohydramnios, high blood glucose levels during 6 to 7 months of pregnancy and a history of cord looping around the neck of the fetus at 33 weeks of gestation. There was no reported history of toxoplasma or rubella. There is no history of radiation exposure or drug use during pregnancy. No reported maternal history of fever or genitourinary infections during the pregnancy. No history of abortions. There is no history of cryptophthalmos or other significant abnormalities in immediate or distant families. The neonate weighed 3416 g at birth. Neonate cried immediately after birth, with no history of seizures or jaundice. History of NICU admission for 2 days due to respiratory difficulty.

On inspection, there is an absence of eyelid, eyebrow and eyelashes in the right eye, collectively known as adnexal structures (Figure 1). The left eye was apparently normal. There was no history of any other developmental abnormalities, that is, the head circumference, anterior fontanelle, and nasal bridge were normal. There were no significant findings in the head-to-toe examination. No other congenital defects of the ears, respiratory system, or fingers existed. The auditory and motor examinations were found to be normal.

B-scan ultrasonography for both eyes was done (Figure 2). The right eye B scan revealed the absence of a posterior chamber and membranous lens, a shallow anterior chamber, and a posterior staphyloma. B Scan of the left eye revealed a central flat anterior chamber and the presence of a posterior chamber. The Chest X-ray was normal. USG revealed mild hydronephrosis in the right kidney and irregular urinary bladder walls.

A diagnosis of unilateral complete cryptophthalmos was made after ruling out possible differential diagnoses, which include ankyloblepharon (partial or complete adhesion of the ciliary edges of superior and inferior eyelids), blepharophimosis (narrowing of the eye-opening) and symblepharon (partial or

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complete adhesion of the palpebral conjunctiva of the eyelid to the bulbar conjunctiva of the eyeball). we also suspected the possibility of Fraser's syndrome, but molecular genetic testing was not performed due to low resource settings. Surgical reconstruction was recommended for cosmetic purposes but was refused by the parents.

Discussion

Cryptophthalmia is of 3 types: Complete type, incomplete type and abortive type.[6] Complete cryptophthalmos is the condition where the skin entirely envelops the eye, the adnexal structures like the eyebrow and eyelid are absent, and the eye is staphylomatous, microphthalmic, or normal. Partial cryptophthalmos shows the absence of the nasal part of the eyelid fold, and the skin encroaches onto the cornea on the nasal side. The anterior segment structures are formed. Abortive cryptophthalmos, also called congenital symblepharon, is a condition where the upper eyelid may be partially or completely absent and the lower lid is normal.[7] Cryptophthalmos may also be classified as isolated cryptophthalmos or cryptophthalmos sequence and cryptophthalmos syndrome. Cryptophthalmos can occur as an isolated trait, part of a sequence of developmental abnormalities or part of a syndrome. The inheritance pattern depends on the underlying cause, with isolated cryptophthalmos reported as an autosomal dominant trait and cryptophthalmos syndrome having an autosomal recessive mode of inheritance.[2]

Cryptophthalmia may occur sporadically or familial. In familial cases, vertical transmission is seen.[1] Autosomal recessive inheritance is most common in familial cases, although autosomal dominant and X-linked inheritance has also been reported.[1] Isolated cryptophthalmos is rare, and very few cases have been reported so far. The prominent differential diagnosis would be cryptophthalmos, ankyloblepharon, blepharophimosis, and symblepharon. Ankyloblepharon is characterized by the fusion of 2 eyelids, partially or completely, and the other parts of the eye tend to be normal. This can be ruled out in our case since no adnexal structures are developed in the right eye.[8] Blepharophimosis indicates underdeveloped eyelids, but in this case, the eyelids of the right eye are completely absent. Maternal deprivation of vitamin A is often considered to be one of the etiologies.[1]

A large number of cryptophthalmia cases are associated with Fraser syndrome.[9] Fraser syndrome is inherited in an autosomal recessive pattern, and FRAS1, FREM2 and GRIP1 genes have been identified to cause Fraser syndrome.[10] Fraser syndrome 1 is caused by a mutation in the FRAS1 gene located on chromosome 4q21.[11] Fraser syndrome 2 is caused by a mutation in the FREM2 gene (present on chromosome 12q14), and Fraser syndrome 3 is caused by a mutation in the GRIP1 gene (present on chromosome 12q14).[12,13] Most of the reported cases are in neonates and young children, and one rare case of Fraser syndrome in an adolescent has been recently reported.[14]

Table 1. The diagnostic criteria for Fraser syndrome.

MAJOR CRITERIA	MINOR CRITERIA
Cryptophthalmos	Congenital Malformation of Nose
Syndactyly	Congenital Malformation of Ears
Urogenital abnormalities	Congenital Malformation of the larynx
Sib with Fraser syndrome	Cleft lip and/or palate
	Skeletal defects
	Umbilical hernia
	Renal agenesis
	Mental retardation

Figure 1. Neonate with the absence of right eyelid (cryptophthalmos).

Two major criteria and one minor criterion or one major criterion and at least 4 minor criteria are required for the diagnosis of Frasers syndrome (Table 1).[3] In our case, the patient has cryptophthalmos and irregular bladder walls [urogenital abnormality], confirming 2 major criteria. Still, no symptom from the minor criteria was observed, and a theoretical diagnosis of Frasers syndrome was made without molecular confirmation. In a study done by Slavotinek and Tifft, 88 out of 117 [75%] satisfied the diagnostic criteria for Fraser syndrome. When they observed the gestational reports of the patients, 20 out of 117 reported oligohydramnios, and the majority of them were born at term.[3] The study also highlighted the clinical variability associated with Fraser syndrome and the potential genetic heterogeneity of the condition. The presence of patterns of anomalies seen in other syndromes without cryptophthalmos suggests the

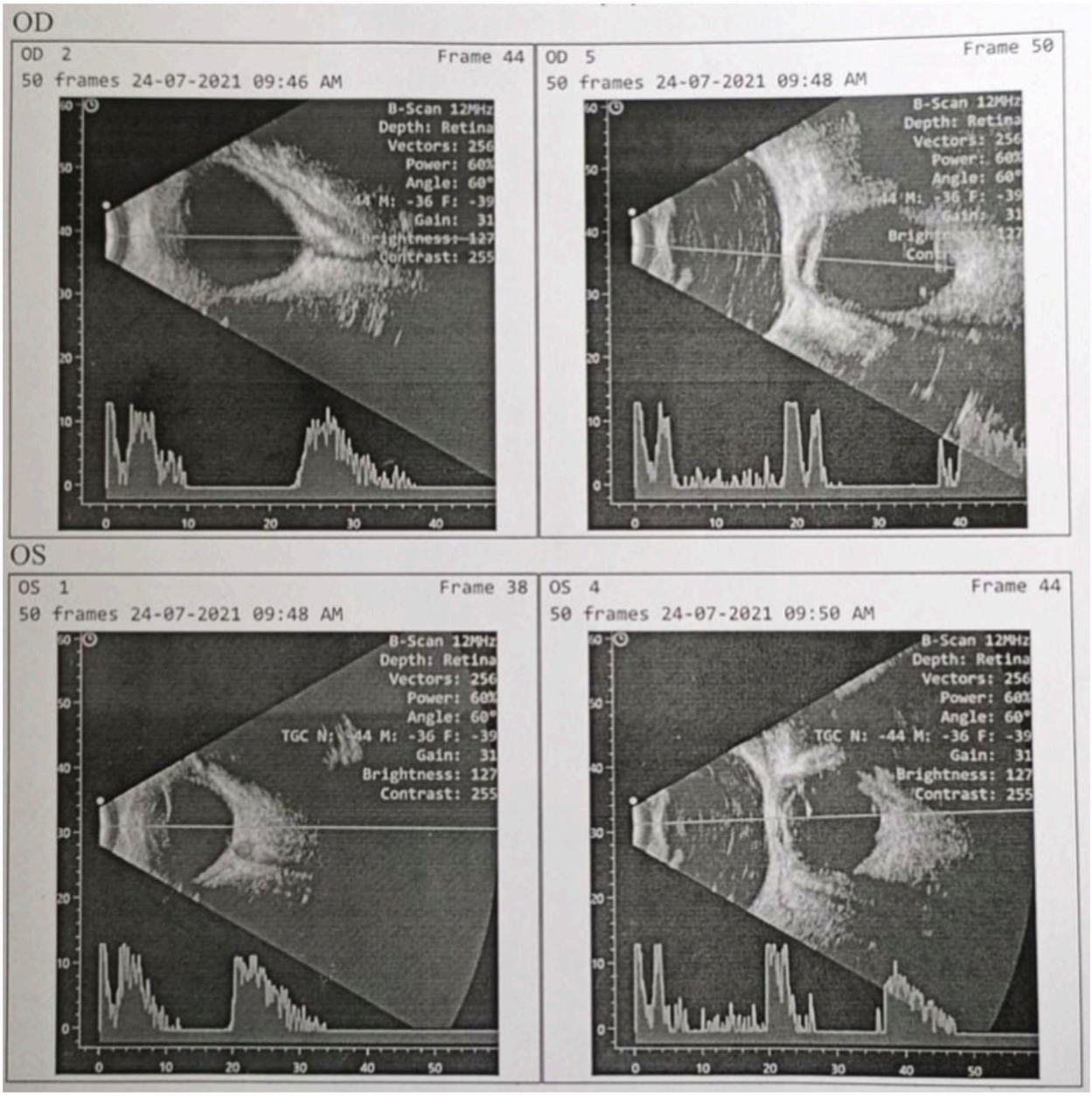

Figure 2. B Scan ultrasonography showing features of Right eye (OD) and left eye (OS).

involvement of common modifier genes in the phenotypic variation of Fraser syndrome. These findings contribute to a better understanding of the clinical presentation and potential genetic mechanisms underlying Fraser syndrome.[3] These reports indicate a possibility of Frasers syndrome even with ambiguity in the diagnostic criteria. In our case, a molecular genetic test might confirm the diagnosis of Fraser syndrome, but not conducted due to low resource settings.

Orbital reconstruction with corneal grafting and anterior vitrectomy (to remove the vitreous gel from the anterior portion of the eye) and lid reconstruction is done in a few cases. Still, the visual deficit usually persists, but there will be a cosmetic improvement. As per the parent's decision, surgical intervention was not pursued due to the poor visual prognosis. We advised prenatal genetic screening and testing for future pregnancies. These findings suggest the importance of genetic counseling and testing in cases of cryptophthalmos to identify potential genetic mutations and facilitate appropriate management.

Conclusion

In conclusion, we report a rare case of complete cryptophthalmos and suspected Fraser's syndrome in a female neonate. Some congenital malformations cannot be identified through routine prenatal screening. Further studies are needed to explore this syndrome's genetic heterogeneity and identify possible modifier genes that may explain the phenotypic variability associated with Fraser's syndrome.

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Author Contributions
Rithika Ramadugu - substantial contribution to the concept or design of the article, Approved the version to be published; AND, agreed to be accountable for all aspects of the work. Satwik Kuppili - Drafted the article or revised it critically for important intellectual content; AND substantial contribution to the concept or design of the article, Approved the version to be published; AND, agreed to be accountable for all aspects of the work. Tarun Kumar Suvvari - Drafted the article or revised it critically for important intellectual content; AND substantial contribution to the concept design of the article, Approved the version to be published; AND, agreed to be accountable for all aspects of the work. Vindhya V Lella - Drafted the article or revised it critically for important intellectual content; AND, agreed to be accountable for all aspects of the work. Vimal Thomas - substantial contribution to the concept or design of the article, Approved the version to be published; AND, agreed to be accountable for all the work.

Informed Consent
Written informed consent was obtained from the patients' mothers for the research and the publication.

Ethics Statement
In our university, Ethics approval was not required for case reports and case series.

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