Original Article

Clinical features and orbital anomalies in Fraser syndrome and a review of management options

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Purpose: Fraser syndrome is a rare congenital disorder comprising cryptophthalmos, syndactyly, and many times, urogenital anomalies. Herein, the authors aimed to study and report the clinical features and orbital anomalies in cases diagnosed with Fraser syndrome. **Methods:** The authors retrospectively evaluated the records of patients with Fraser syndrome who had presented to a tertiary eye care hospital in northern India in the last 2 years (from January 2019 to December 2020). The clinical features were studied, entered in MS Excel, and the data was evaluated. **Results:** Data of 15 patients with Fraser syndrome were found. Majority of the patients were males and presented in the pediatric age group. Bilateral involvement was more common, and the most common variant of cryptophthalmos was abortive. Complete and medial madarosis of the eyebrows was the most common periocular finding. Complete cryptophthalmos was associated with cystic globes, whereas abortive forms had superior symblepharon. Common systemic features included syndactyly, bifid nose, and urogenital anomaly. **Conclusion:** Fraser syndrome is an extremely rare developmental disorder; it encompasses a wide range of ocular, periocular, and orbital anomalies, along with multiple pre-existing systemic anomalies. The treating ophthalmologist should always be careful in examining these patients.

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Cryptophthalmos, or hidden eye, was first described by Zehender in 1872.[1] It is a rare congenital disorder affecting the eyelids. In 1969, Francoise *et al*.[2] classified it as complete, incomplete, and abortive based on the severity of the disease manifestation. In a complete cryptophthalmos, both upper and lower eyelids are replaced by a sheet of skin that extends from forehead to cheek; eyebrows and eyelashes are poorly developed with grossly malformed ocular structures and associated microphthalmos. Incomplete or atypical cryptophthalmos is characterized by poorly defined palpebral fissure and rudimentary conjunctival sac, poorly developed globe, and microphthalmos. The abortive variant is also known as congenital symblepharon type, where the lower lid is normal and the upper lid covers the upper cornea and adheres to it by a symblepharon. There can be keratinization and vascularization of the cornea, making it a sight-threatening situation. In 1962, George Fraser put forward a theory of autosomal recessive inheritance in these patients; since then, it has been known as Fraser syndrome (FS). The syndrome consists of various ocular and systemic abnormalities.[3] The clinical entity, being rare, has limited literature from the Indian subcontinent; therefore, we conducted a retrospective study in a tertiary care center of northern India to understand the associated ocular, periocular, and orbital anomalies.

Methods

The patients who were diagnosed with FS in the oculoplastic department of a tertiary eye care center in North India over a period of 2 years (January 2019-December 2020) were considered for the study. The clinical features, particularly emphasizing the ocular, periocular, and orbital findings of all these patients, were entered in MS Excel and the data was analyzed.

Results

On the retrospective evaluation of the medical records, 15 diagnosed cases of FS were found [Table 1]. On analysis of 15 patients, an obvious male preponderance was seen (M:F- 4:1). The frequency of bilateral cases was twice that of unilateral cryptophthalmos. Among all the eyes, abortive cryptophthalmos (n = 13) was the most common, followed by complete (n = 8) and incomplete (n = 4) cryptophthalmos. Among unilateral cases, abortive cryptophthalmos was the most common (n = 4), whereas in bilateral cases, complete and abortive cryptophthalmos had equal frequency (n = 4 each). All the complete cryptophthalmos were bilateral. Only one patient had bilateral incomplete variety, and one patient had incomplete

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and abortive cryptophthalmos, one on each side. The mean age of presentation was 4.5 years (range 2 months-19 years). More than 50% presented before 1 year of age ($n = 8$). All the patients who presented at an age ≥5 years had abortive cryptophthalmos. History of consanguineous marriage in parents was seen among three patients. Among congenital malformations, the order of incidence included syndactyly ($n = 9$); nasal abnormalities in the form of bifid nose ($n = 8$) and high nasal alae ($n = 1$; urogenital abnormalities ($n = 4$); gastrointestinal abnormalities like esophageal web ($n = 1$), laryngoesophageal web ($n = 1$), and omphalocele ($n = 1$); and facial hemangioma ($n = 1$). Eyebrow abnormalities were commonly seen in the form of complete madarosis ($n = 11$), medial madarosis ($n = 2$), abnormal and faint eyebrows ($n = 2$). Other periocular abnormalities like frontonasal dysplasia ($n = 3$), telecanthus ($n = 1$), and lacrimal drainage abnormalities like dacryocele and lacrimal duct obstruction ($n = 2$) were noted. All complete cryptophthalmic eyes had cystic globe with a sheet of skin extending from eyebrow to cheek [Fig. 1]. Among four eyes incomplete variety, three eyes had cystic globes (one unilateral case had central depression in the globe) and one eye had superior symblepharon [Fig. 2]. All abortive cryptophthalmos patients had medial symblepharon with coloboma [Fig. 3]. Two patients in abortive cryptophthalmos (one unilateral and one bilateral) had undergone coloboma repair for cosmetic purpose. The other eye was normal in all the unilateral cases. In cases of complete cryptophthalmos, an attempt was made for forming the eyelid along with ocular surface reconstruction. Surgery was planned in cases that showed movement of the cystic structure indicating the possibility of a formed eyeball with some extraocular muscles.

Abortive cryptophthalmos patients who had eyelid coloboma with symblepharon underwent a lid reconstruction along with amniotic membrane grafting (AMG). The choice of reconstructive procedure was made on the basis of the size of the eyelid coloboma. In case of a shallow coloboma, margins were freshened and direct closure was done, whereas in situations with a large upper eyelid defect, a two-staged lid-sharing procedure, namely Culter-Beard, was performed.

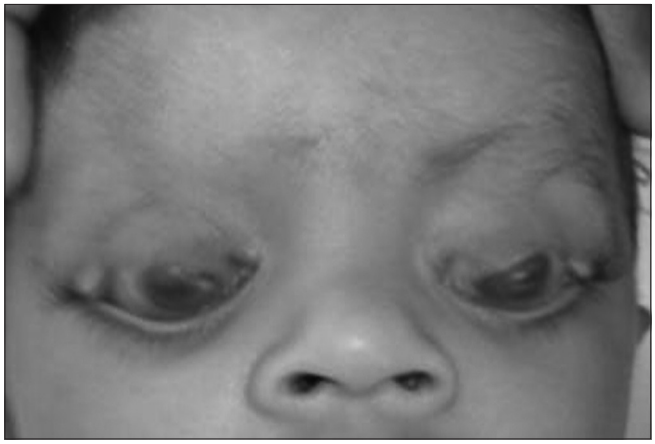

Figure 1: Clinical picture of a patient with Fraser syndrome with complete cryptophthalmos

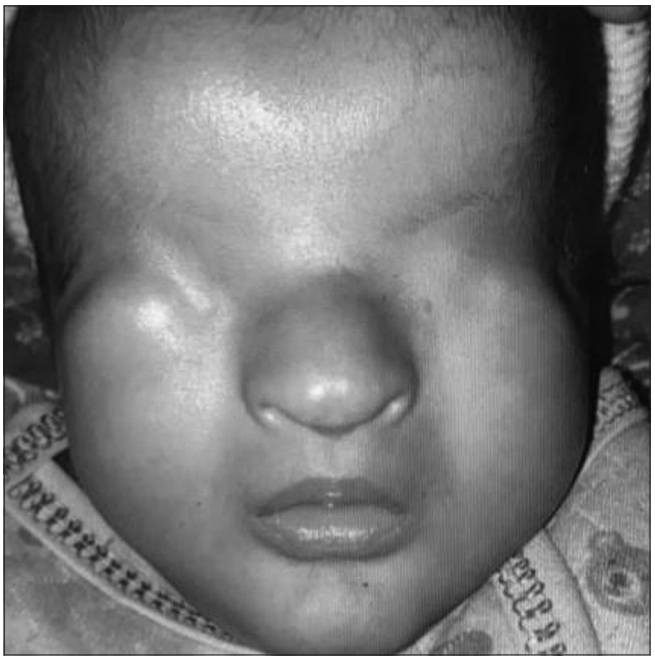

Figure 2: Clinical picture of a patient with Fraser syndrome with incomplete or partial cryptophthalmos

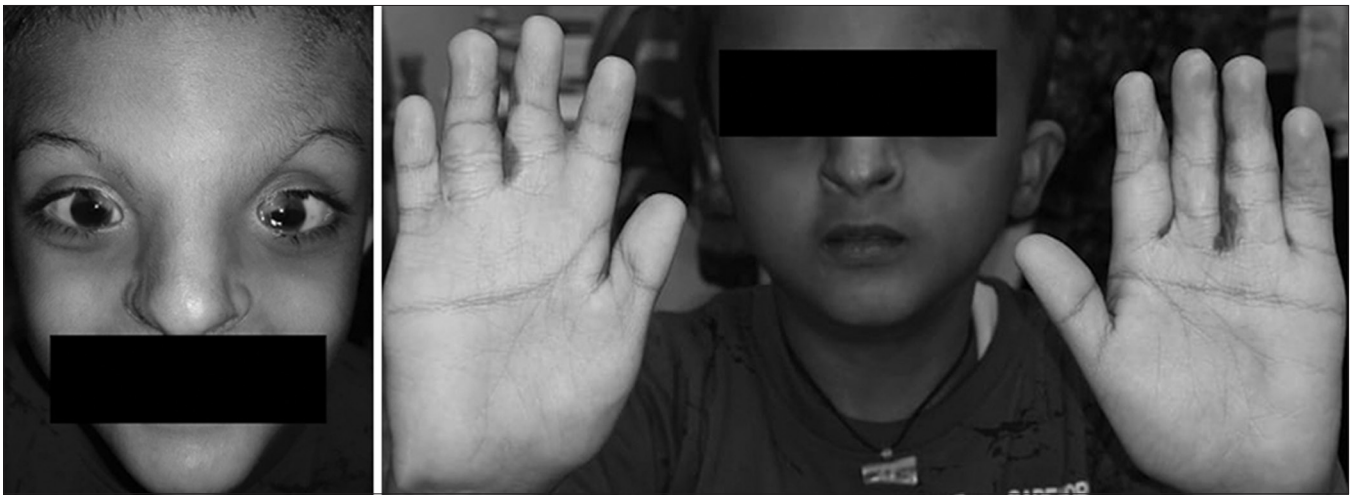

Figure 3: Clinical picture of a patient with Fraser syndrome with abortive cryptophthalmos with syndactyly

Table 1: Clinical details of the patients

	Age/sex	Systemic features	Periocular features	Eyelid abnormalities	Ocular features		Management
					Right eye	Left eye	
Patient 1 (bilateral complete)	6 months/M	Syndactyly	Eyebrow madarosis Frontonasal dysplasia Swelling in the right side	No eyelids	Cystic globe Some visible movements	Cystic globe	Globe exploration of the right eye with AMG-covered shell conformer placement. Left eye was not touched
Patient 2 (bilateral complete)	3 months/M	Urogenital anomaly Bifid nose Consanguineous marriage	Faint eyebrow Frontonasal dysplasia Swelling in the right side	No eyelids	Cystic globe	Cystic globe	Both eye globes' exploration with AMG-covered shell conformer placement and fornix formation
Patient 3 (unilateral abortive)	3 months/F	Urogenital anomaly Facial hemangioma	Eyebrow madarosis	Upper eyelid coloboma	Superior symblepharon	Normal	Symblepharon release with AMG-covered symblepharon ring placement with Cutler-Beard staged procedure
Patient 4 (unilateral abortive)	8 years/F	Syndactyly High nasal ala	Eyebrow madarosis	Upper eyelid coloboma	Superior symblepharon	Normal	Symblepharon release with AMG-covered symblepharon ring placement with Cutler-Beard staged procedure
Patient 5 (bilateral incomplete)	10 months/M	Syndactyly Bifid nose	Bilateral eyebrow madarosis	Bilateral lateral lower eyelids with cilia	Cystic globe	Cystic globe	Globe exploration with AMG with symblepharon ring placement of right eye. Left eye untouched
Patient 6 (right abortive left incomplete)	6 months/M	Syndactyly Omphalocele Laryngoesophageal webs	Abnormal eyebrows Left-sided dacryocele	Right eye superomedial coloboma Left eye absent eyelids	Superonasal symblepharon	Cystic elevation with a central depression	Untouched/no procedure
Patient 7 (bilateral complete)	2 months/F	Bifid nose Urogenital anomaly Syndactyly	Eyebrow madarosis	Absent eyelids	Cystic globe	Cystic globe	Untouched/no procedure
Patient 8 (bilateral abortive)	8 years/M	Syndactyly	Medial eyebrow madarosis Naso lacrimal duct obstruction Telecanthus	Medial coloboma	Superonasal symblepharon	Superonasal symblepharon	No intervention
Patient 9 (bilateral complete)	11 months/M	Bifid nose Urogenital anomaly	Eyebrow madarosis	Absent eyelids	Cystic globe Movements visible	Cystic globe	Bilateral globe exploration with AMG
Patient 10 (bilateral abortive)	6 years/M	Syndactyly Bifid nose	Eyebrows madarosis	Repaired coloboma	Superior symblepharon	Superior symblepharon	Bilateral Cutler-Beard
Patient 11 (unilateral abortive)	5 years/M	Bifid nose	Normal	Superomedial coloboma	Normal	Superior symblepharon	Left eye upper lid coloboma direct repair with AMG for fornix formation
Patient 12 (unilateral incomplete cryptophthalmos)	2 years/M	Esophageal web Syndactyly Consanguineous marriage	Telecanthus Frontonasal dysplasia	Superomedial coloboma	Superior symblepharon	Normal	Medial canthoplasty with AMG with symblepharon ring placement

Contd...

Table 1: Contd...

	Age/sex	Systemic features	Periocular features	Eyelid abnormalities	Ocular features		Management
					Right eye	Left eye	
Patient 13 (bilateral abortive)	16 years/M	Bifid nose	Medial eyebrow madarosis	Superomedial coloboma	Superior symblepharon	Superior symblepharon	Bilateral symblepharon release with AMG with symblepharon ring placement
Patient 14 (bilateral abortive)	6 months/M	Bifid nose Consanguineous marriage	Normal	Superior coloboma	Superior symblepharon	Superior symblepharon	Outside operated Cutler-Beard procedure with evisceration. No intervention
Patient 15 (unilateral abortive)	19 years/M	Syndactyly	Normal	Repaired coloboma	Contracted socket	Normal	Both eyes Cutler-Beard procedure

AMG=amniotic membrane grafting

Two eyes of patients with bilateral complete cryptophthalmos underwent globe exploration with ocular surface reconstruction using AMG-covered conformer shell placement. Remaining eyes were left untouched as the guardians refused to operate when explained regarding the risks of the surgery and the prognosis. Eyes with incomplete cryptophthalmos also underwent ocular surface reconstruction using AMG along with fornix formation and placement of a conformer. One patient underwent telecanthus repair using Y-V plasty with medial canthal tendon plication.

Discussion

FS (OMIM #219000) is named after George Fraser, who first described the clinical features of cryptophthalmos-syndactyly syndrome in 1962.[4] The diagnosis is made on the basis of presence of clinical features categorized into major (cryptophthalmos, syndactyly, ambiguous genitalia, urinary and respiratory tract anomalies, and an affected sibling) and minor (congenital nose and ear malformations, skull ossification defects, anorectal anomalies, and umbilical hernia) criteria, which were suggested by Thomas *et al*. in 1986 and later modified by van Haelst and the Fraser Syndrome Collaboration Group in 2007.[5,6]

The incidence of this condition is extremely rare, as a large population study in the European population revealed an estimated number of 0.2 cases per 100,000 births.[7] Although various theories have been put forward by different authors for cryptophthalmos, the most convincing one is a failure of primary differentiation, which occurs during embryogenesis.[4] Thomas *et al*. reviewed 124 cryptophthalmos cases in 1986 and found no gender predilection; his findings hinted toward an autosomal recessive mode of inheritance.[6] van Haelst *et al*.[5] documented 85% of true cryptophthalmos in their study, which included 59 patients of FS. Seventy-eight percentage of them had complete bilateral cryptophthalmos, and abnormal frontal hairline was found in 17% of cases. All cases with abnormal hairline had associated ocular and periocular anomalies, namely eyelid coloboma and cryptophthalmos. Saleh *et al*.[8] studied 13 eyes from seven cases of FS and found that 10 of these eyes had abortive cryptophthalmos while the remaining 3 had complete cryptophthalmos. In our study, we found that the mean age of presentation was 4.5 years and there was an obvious male predilection among the cases. The number of abortive cases was more than those of complete and incomplete types. All the cases of complete cryptophthalmos were bilateral.

The management options for ocular, periocular, and orbital anomalies in FS vary according to the type of cryptophthalmos, facial abnormality, and orbital defects. Abortive cryptophthalmos, which is also known as congenital symblepharon type, can present with keratinization of the cornea, which can lead to diminished vision. The affected cases also have restricted ocular mobility. Hence, prompt management, follow-up, and surgical intervention are advised in the pediatric age group.

Complete cryptophthalmos, which is associated with developmental abnormalities of the globe, can give rise to glaucoma and a painful blind eye. If there is no visual potential, the management is aimed at cosmesis.[9] Saleh *et al*.,[8] in their study on correction of cryptophthalmos, aimed at creating lids and fornice reconstruction with muscle or skin flaps in cases of

complete cryptophthalmos, while in cases of abortive form, they aimed to preserve the visual potential. Removal of adhesion from the cornea, mucus membrane graft, eyelid switch flap, etc., were used for the same. Six out of 10 eyes of abortive cryptophthalmos achieved better ocular surface post-surgery. In complete cryptophthalmos, the main objective is to form a conjunctival sac, which is done as a two-step procedure. A horizontal skin incision along with placement of a mucus membrane-covered conformer is later followed by reconstruction of upper and lower lid lamellae after 1 year of the initial surgery.

In case of incomplete variety, the target is to achieve a better cosmesis of both upper and lower eyelids with the help of skin or cartilage grafts, so that in case the eye does not achieve vision later in life, a potential space will be present to place the conformer. In case of abortive cryptophthalmos, which has relatively better visual outcome when compared to its counterparts, the main aim is to protect the ocular surface. To achieve the same, oral mucosal membrane grafts and hard palate grafts have been used. Some authors propose the use of lower eyelid Mustarde-type switch flap for upper eyelid correction.[10]

Markal *et al*.[11] have reported a case of a 16-year-old female with abortive cryptophthalmos, who had nasal deformities, ear cup deformity, syndactyly, and mild clitoromegaly. The parents were consanguineous, and one of the siblings had retinal pathology and another sibling was stillborn. The cryptophthalmos was managed by synechiae release, dividing the skin attachments and apposing the wound edges with primary sutures.

Various authors have mentioned the use of buccal mucosal graft in oculoplastic surgeries with a favorable outcome. Weng *et al*. have described the use of buccal mucosa for covering the raw surfaces of lid margins to prevent adhesions in case of incomplete cryptophthalmos correction.[12] In the present scenario, an AMG is being widely used in the management of ocular surface diseases and also in reconstructive procedures. Stewart *et al*., in their study, had mentioned the use of AMG for reconstruction of fornix and upper lid in case of partial cryptophthalmos, which provided satisfactory results.[13] The advantage of AMG over buccal mucosal graft is that the metabolic demand is less when compared to the latter, which implies a lesser chance of rejection.[13] Amniotic membrane acts as an anatomical barrier, such that it prevents adhesions between surfaces; also, it promotes epithelialization and has anti-inflammatory properties.[14] Ding *et al*.,[15] in their study on surgical correction of abortive cryptophthalmos, had pointed out the effective use of scleral and amniotic graft for the reconstruction of upper lid and fornices. To reduce allergic reaction, for better wound apposition, and to reduce the operating time, fibrin glue is preferred over suturing in placing the AMG.[16]

Conclusion

We thereby conclude that the demographic profile of patients with FS in the Indian subcontinent is different from that of the European population. The condition is rare and is associated with a multitude of systemic congenital anomalies. It requires proper counseling of the attendants regarding the prognosis and a multidisciplinary approach to impart cosmesis**.**

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Conflicts of interest

There are no conflicts of interest.

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