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CLINICAL CASE REPORT

Report on ocular biometry of microphthalmos, retinal dystrophy, flash electroretinography, ocular coherence tomography, genetic analysis and the surgical challenge of entropion correction in a rare case of Hallermann–Streiff–Francois syndrome

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Abstract
Purpose To report new aspects of the phenotype including Retinal dystrophy and surgical challenges in Hallermann-Streiff Francois syndrome (HSFS).
Methods Detailed phenotype of a female with HSFS was evaluated including skeletal changes, comprehensive eye examination, detailed ocular biometry, electroretinography and macular Ocular coherence tomography. Surgical notes of lid surgery for entropion were reviewed. Genetic screening was also done.
Results Unique Ocular biometry with electroretinography changes, macular folds and fundus changes suggestive of an unreported Retinal dystrophy in a typical patient with HSFS were noted. Surgery was challenging both due to difficulty in endotracheal intubation anaesthesia because of the dento-facial abnormalities and the skin fragility.
Conclusion This report provides additional information especially pigmentary retinal dystrophy, macular folds and electroretinography in HSFS. The microphthalmos had overlapping posterior segment findings usually reported with Nanophthalmos and Posterior microphthalmos. The surgical difficulties and outcomes of the rarely encountered adnexal abnormalities emphasize the need for a multi disciplinary approach for appropriate management.

Introduction

Hallermann–Streiff–Francois syndrome (HSFS), mainly constituting ocular and facial abnormalities, is a rare syndrome [1–3]. Seven essential features (Table 1) were described by Francois [2]. However, there are very few descriptions of the full phenotype. We report a 22-year-old lady who presented with swelling, irritation and watering in the left eye of 3 months duration. She had a significant past history of bilateral congenital cataract surgery at 3 months of age. She was born to non-consanguineous, unaffected parents and had two normal siblings. Detailed phenotyping for ocular structural and functional parameters

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Table 1 Diagnostic criteria for Hallerman–Streiff–Francois syndrome

1. Dyscephalia and bird face
2. Dental anomalies
3. Proportionate nanism(dwarfism)
4. Hypotrichosis
5. Atrophy of skin
6. Bilateral microphthalmia
7. Congenital cataract

revealed new signs. We also discuss the genetic evaluation and the difficulties of lid surgery in our patient.

Materials and methods

Clinical examinations were performed at the L V Prasad Eye Institute, and the Molecular genetic analysis was performed at the Centre for DNA Fingerprinting and Diagnostics, Hyderabad, India. After obtaining the written informed consent, detailed ocular and systemic evaluation of the proband and genetic evaluation from blood samples of the parents and the proband was done ophthalmological examination included best corrected visual acuity (BCVA), Goldmann applanation tonometry, gonioscopy, slit-lamp biomicroscopy and dilated fundus examination. Spectral-domain optical coherence tomography (SD-OCT) of macula and autofluorescence was performed; full-field electroretinogram (ERG) was recorded from both the eyes using the Metrovision Monitor (France) in accordance with the standards of International Society of Clinical Electro-physiology of Vision (ISCEV) [4]. LVPEI zari electrode placed close to the lower corneal limbus was used.

Full-field electroretinogram was performed after pupillary dilatation, using a Ganzfeld stimulator. Dark-adapted ERG responses (rod response, maximal response and oscillatory potentials) were obtained after 20 min of dark adaptation and light-adapted responses (cone response and 30 Hz flicker) after 10 min of light adaptation to the background luminance of 22 cd/m^2.

Genetic evaluation from blood samples of the parents and the proband was done using flanking primers for the 'Gap junction protein, alpha 1, 43 kDa' (GJA1) gene.

Results

Case report

A 22-year-old lady presented with swelling, irritation and watering in the left eye of 3 months duration. She weighed 30 kg, had proportional dwarfism and a height of 130 cm. There was aphakia following congenital cataract surgery, severe and generalized alopecia, atrophic skin, brachycephaly, micrognathia, parrot beak nose and hypodontia (Fig. 1).

Best corrected visual acuity was 20/125 OD and 20/400 OS with +15 D sphere in both eyes. Cycloplegic refraction was +24 D sphere, but this higher correction did not improve the visual acuity any further. Ocular motility showed nystagmus, alternating exotropia and dissociated vertical deviation with the left eye predominantly fixating. The left eye had both upper and lower lid entropion and lower lid trichiasis. Both the eyes had blue sclera, small horizontal corneal diameter (9 mm), borderline raised intraocular pressure (24 mmHg, applanation tonometry), normal Central Corneal Thickness (503 μm), diffuse punctate subepithelial corneal opacities, linear full thickness surgical corneal scar superiorly, deep and quiet anterior chambers, sluggishly reacting pupils and aphakia with absent posterior capsules. Gonioscopy showed open angles with patchy peripheral anterior synechiae in both the eyes.

Fundus examination of both eyes showed (Fig. 2a) small crowded discs, cup disc ratio of 0.1, normal retinal vessels and media haze 1 + due to corneal scarring. There was bilateral altered macular pigmentation and patchy hypopigmented areas around the disc extending to the arcades. The left eye also showed macular folds and choroidal folds. The scotopic flash ERG showed decrease in b-wave amplitude and prolonged implicit time of the isolated rod response with moderately increased amplitude and normal implicit time of the b-wave in maximal combined response (Fig. 2b; Table 2). Photopic responses were near normal. Nystagmus precluded reliable pattern ERG recording.

B-scan ocular ultrasonography (Fig. 3a) showed thickened choroid 1.9 mm OD and 1.88 mm OS (normal 1.3 ± 0.2 mm) and bilateral 0.95 mm thickened sclera (normal 0.63 ± 0.38 mm) [5]. Detailed ocular biometry showed reduced axial length of OD 15.38 mm and OS 15.00 mm. Keratometry was steep;

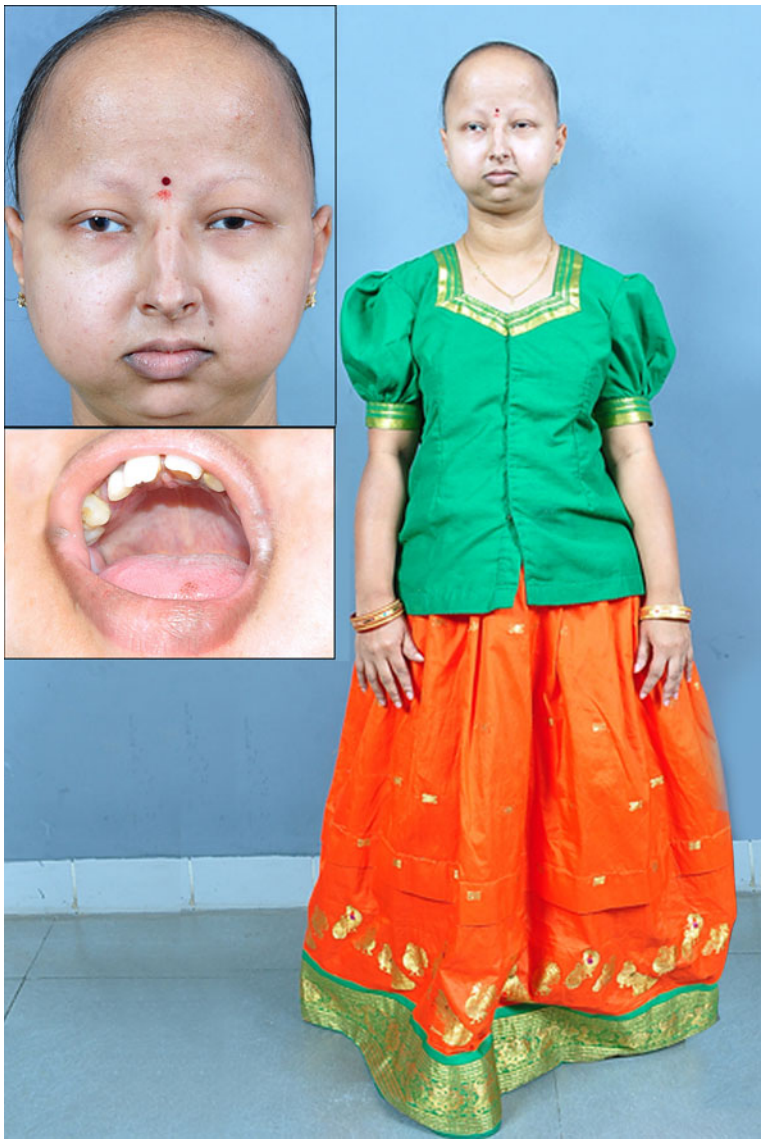

Fig. 1 Showing the skeletal and facial features of the proband

the right eye was K1 55.54 at 86° K2 56.73 at 176°; and left eye was K1 54.04 at 160° and K2 56.08 at 72°. SD-OCT of both eyes showed thickened neurosensory retina with dry elevated macular fold with normal retinal pigment epithelial layer (Fig. 3b). Fundus autofluorescence was difficult to visualize due to corneal haze, but was grossly normal in both eyes. Visual fields were attempted, but were unreliable possibly due to the low vision.

To address her current symptoms, after written consent, the patient underwent surgical correction of the left eyelid abnormalities. Inhalational anaesthesia with a laryngeal mask was used because of difficult intubation. This appeared to be due to the micrognathia and the forward displacement of the temporomandibular joint. Intraoperative observations included extremely fragile skin, shortened and fibrosed upper tarsal plate, normal lower lid tarsus and fatty infiltration of the lower lid retractors. Upper lid entropion was corrected by tarsal fracture and everting sutures while lower lid entropion was corrected by Jones procedure. Intraoperatively due to the fragile skin, tissue handling and suturing was challenging. She was asymptomatic at 3 months of uneventful follow-up.

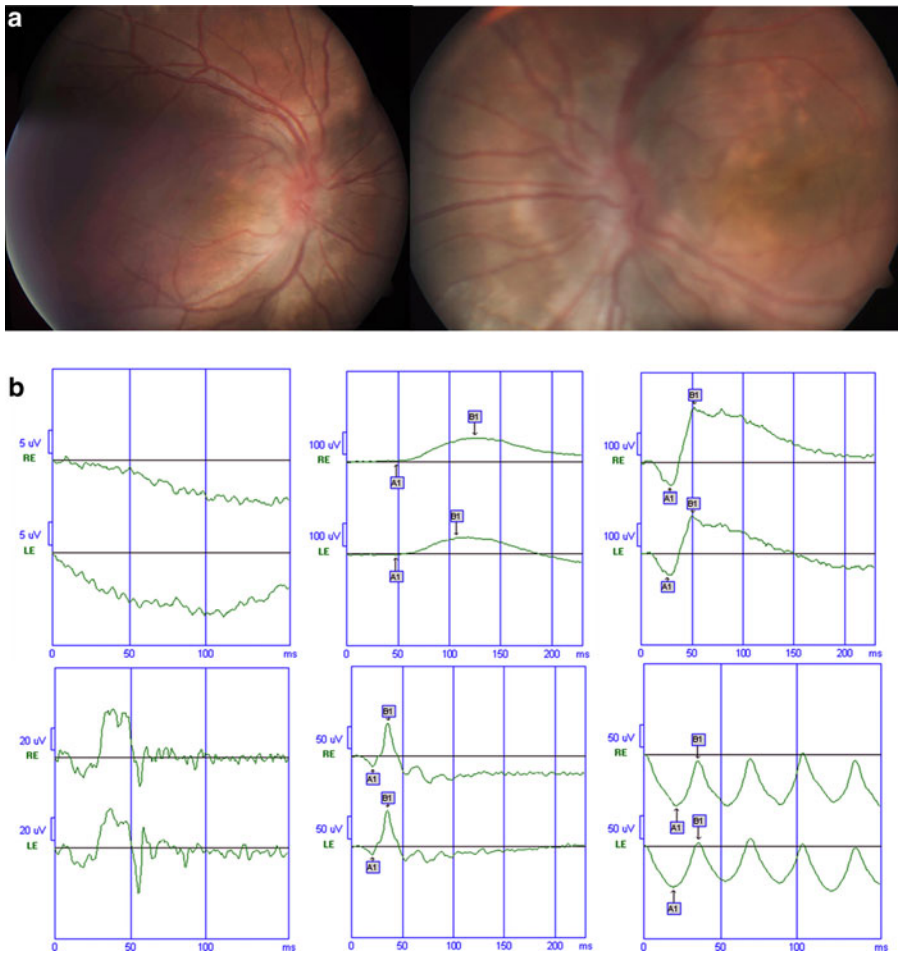

Fig. 2 **a** Fundus photograph showing bilateral pigmentary retinal dystrophy, **b** Electroretinogram of the proband

Intraocular pressure was lowered to 15 mmHg by topical timolol maleate 0.5 % eye drops twice a day.

The proband's blood sample revealed a normal 46, XX karyotype. DNA sequencing was done using flanking primers for GJA1 gene since this gene is involved in the closely related condition of Oculodentodigital dysplasia (ODDD). Multiple heterozygous sequence variations were noted in the proband in GJA1 gene, and all these were also found in either of the normal parents and so were unlikely to be pathologic mutations. They were likely to be due to amplification of the pseudogene (rhoGJA1).

Discussion

Our case fulfilled all the 7 criteria of this rare condition [2] and had many of the typical ocular features reported in HSFS including microcornea, corneal opacities and bilateral congenital cataracts [1–3, 5–7]. However, a few new or rare features were noted that are discussed below.

Ocular alignment

Most of the reported cases had esotropia [6]. Our case had the less commonly reported alternating exotropia with dissociated vertical deviation.

Lid pathology

Entropion has been uncommonly reported [6], but the surgical approach has not been well addressed. Surgical challenges encountered included difficult intubation that was resolved by the use of only a laryngeal mask making it imperative for the surgeon to complete the surgery rapidly. Due to the extremely fragile skin, hypoplastic upper tarsal plate and fatty

Table 2 Flash electroretinogram of the proband

	Right eye		Left eye		Normal range	
	Implicit time	Amplitude	Implicit time	Amplitude	Implicit time	Amplitude
Pattern ERG	0	0	0	0	50	7.5
Scotopic response						
Isolated rod response	124	97.9	106	71.4	88	157
Maximal combined (a-wave) response	27	133	26.1	106	24.3	157
Maximal combined (b-wave) response	49.4	344	48.5	266	49.4	260
Photopic response						
Single cone (a-wave) response	18.9	−20.3	18.9	21.9	18.9	−23.8
Single cone (b-wave) response	34.1	92.1	34.1	92.1	34.3	109
30 Hz Flicker (a-wave)	20.6	103	18.8	83.2	18.2	135
30 Hz Flicker (b-wave)	34.5	91.7	35.1	90.6	33.3	143
Oscillatory potentials	Present					

infiltration of lower lid retractors, very gentle surgical manoeuvres had to be made, making it a technically difficult surgery.

Intraocular pressure

The intraocular pressure was borderline raised (24 mmHg). Trabeculodysgenesis or the past paediatric cataract surgical trauma can predispose the patient to glaucoma in such a condition [8]. The intraocular pressure was medically reduced to normal levels. There was no evidence of glaucoma currently based on the disc appearance, while visual fields could not be reliably done.

Microphthalmos

Though microphthalmia has been widely reported with this syndrome, detailed biometry is rarely reported to characterize the microphthalmia further. Biometric investigations of our patient revealed the presence of thickened retinochoroidal complex and sclera with microcornea, and reduced axial length to <20 mm, suggestive of classical nanophthalmos [9] except cataract which would possibly put the entity as microphthalmos. Nanophthalmos is the terminology used when the corneal diameter is <10.00 mm, and there is no other structural abnormality in an eye with an axial length of <20.5 mm. Any structural abnormality of the eye, example uveal coloboma, in association with reduced axial length is considered as microphthalmia. Presence of cataract has been described in literature as a structural abnormality of the lens and such eyes have been described in the category of microphthalmia. However, whether congenital cataract is a structural, or a biochemical abnormality of the lens is worthy of thought. Structural abnormalities of the lens would probably mean conditions such as lens coloboma, microspherophakia and lenticonus Cataract per se would be more of a biochemical change of the lens protein fibres while the whole lens shape and size are unaffected. Based on the terminology used in literature, due to the presence of congenital cataract, we have labelled the biometric findings as microphthalmos, though in view of the retinal pigmentary changes and the OCT changes described subsequently, the phenotype is more typical of nanophthalmos or posterior microphthalmos [9, 10].

Retinal dystrophy with pigmentary changes

Both hypo- and hyper-pigmented areas suggestive of a diffuse moderately severe retinal dystrophy were seen. Such changes have been reported in association with nanophthalmos and posterior microphthalmos, and not

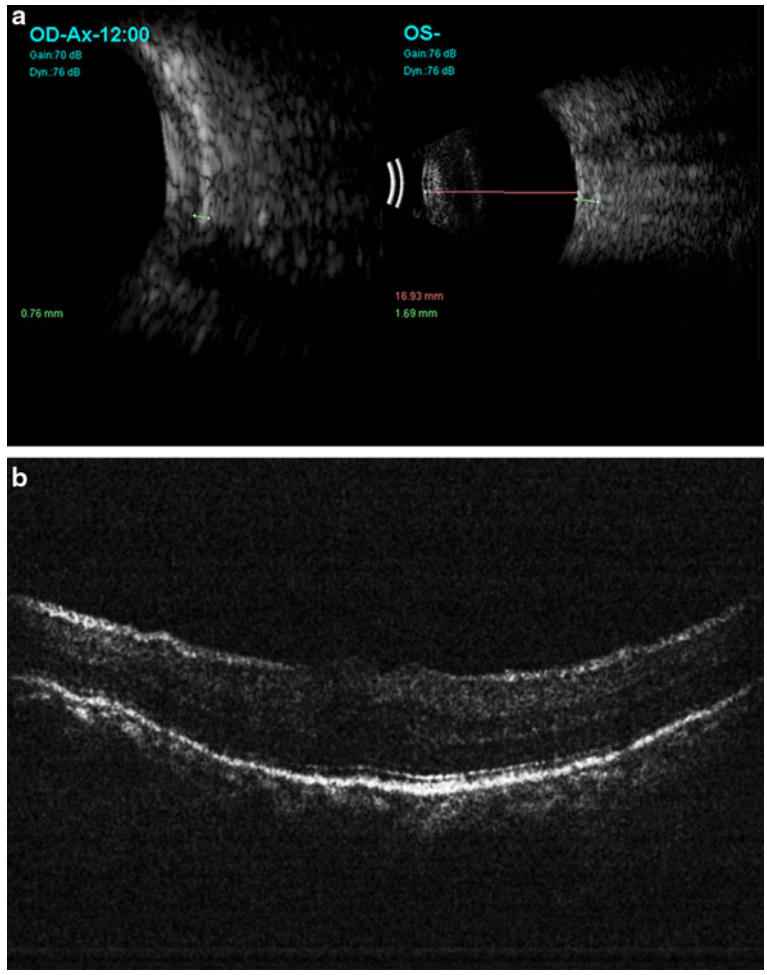

Fig. 3 **a** Bscan ultrasound and **b** OCT showing thickened retinochoroidal complex; thickened neurosensory retina and a dry macular fold

reported in microphthalmos or in HSFS [9, 10]. The changes could also be due to resolved choroidal detachment which might have occurred during cataract surgery [11, 12], though the bilateral symmetrical appearance make this less likely.

ERG

Electroretinogram in HSFS is unreported. In our patient, the scotopic rod-specific ERG amplitude was subnormal. Hyperopic eyes are generally expected to have ERG amplitudes at the upper ends of normal or supernormal parameters [13]. This suggests that there may be a subtle retinal dystrophy that has not been reported in HSFS. The implicit time was within the normal range suggesting that the retinal dystrophy may be relatively non-progressive in nature. Further follow-up may help to evaluate whether the dystrophy is stable or progressive. Patient had no history of nyctalopia or dark adaptation problems currently. She did not complain of progressive deterioration of visual function.

OCT

Changes on OCT were typical of reports in posterior microphthalmos and occasionally in nanophthalmos [9, 10, 14]. Such changes have not been documented in HSFS or in classic microphthalmia previously.

Genotyping

Genetic evaluation in our case and a literature search showed no consistent or well-documented mutation

specific for HSFS. Homozygous mutations in GJA1 are known to result in the ODDD (Oculodentodigital dysplasia) phenotype, a condition closely resembling HSFS, and hence, this gene was selected for genotyping in our study. The GJA1 protein is found in many human tissues such as the eyes, skin, bone, ears, heart and brain. In a single report [15] of Hallerman–Streiff syndrome and GJA1 mutation, the authors themselves expressed doubts about the case being really a typical HSFS.

In conclusion, our report provides additional information especially pigmentary retinal dystrophy and electroretinography, to the existing literature on HSFS. We highlight the presence of unusual type of microphthalmos having overlapping posterior segment findings usually reported with nanophthalmos and posterior microphthalmos. Associated structural and functional features are described in detail. We also report the surgical difficulties and outcomes of the rarely encountered adnexal abnormalities in such patients. We emphasize the need for a multidisciplinary approach for appropriate management. Long-term follow-up is planned to assess any further changes of the associated retinal dystrophy.

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Conflict of interest No conflicting relationship exists for any of the authors. Dr. Subhadra Jalali is a member of the advisory board of Allergan, not connected with the current study.

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