Congoenital Upper Eyelid Coloboma: Embryologic, Nomenclatorial, Nosologic, Etiologic, Pathogenetic, Epidemiologic, Clinical, and Management Perspectives

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Purpose: To review the recent literature and describe the authors’ experience with congenital upper eyelid coloboma.

Methods: In this review, we will summarize the embryologic and etiopathogenetic bases of congenital upper eyelid coloboma, and study the published clinical reports. We will also attempt to briefly shed some light on the rarer syndromic curiosities associated with upper eyelid coloboma.

Results: Congenital upper eyelid colobomas are one of the few nontraumatic oculoplastic emergencies that may occasionally present in the first few days of life with a corneal ulcer and may even present with impending perforation. They can present with or without corneopalpebral adhesions, may be isolated findings or a part of a larger spectrum of congenital anomalies as in the case of Fraser syndrome or Goldenhar syndrome, or could be associated with other rare curiosities that could challenge the clinician with a huge diagnostic dilemma.

Conclusions: Existing literature dealing with congenital colobomas of the upper eyelid is fraught with nosologic problems, confusing etiologies, and overlapping clinical features. We attempted to clarify the salient clinical features, outline the management principles, and until a time in the not-so-distant future where advances in molecular genetic testing would help redefine the etiology and the diverse clinical spectrum of genetic diseases associated with upper eyelid colobomas, we propose a simplified classification scheme based on the relation of the coloboma to the cornea, the presence or absence of systemic features, and all the syndromic and nomenclatorial associations of congenital coloboma of the upper eyelid known today.

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Embryologic and Fetal Development of the Eyelids

Embryonic and fetal eyelid development has been extensively studied elsewhere, but the process of eyelid fusion is of particular relevance for the current discussion. At the beginning of stage 22 (week 8, 54–56 days, 23–28 mm), flattened periderm cells on the eyelid surface undergo a morphogenetic transition into cuboidal epithelium, proliferate, and migrate centripetally toward each other, and thus begin the remarkable process of eyelid fusion. When a connection is established between both eyelids, the periderm cells flatten again to form a continuous sheet ultimately covering the cornea; therefore, the process of eyelid fusion involves 2 coordinated yet distinct processes: epithelial cell migration and proliferation of the epithelium at the migrating edge. In mammals, only the periderm and epidermal layers are involved in eyelid fusion, while eyelid mesenchyme remains distinct in preparation for future
separation.\textsuperscript{14} The exact timing when separation is complete is difficult to deduce from the literature, but in general separation is complete around the sixth or seventh month.\textsuperscript{4,12,22} Recently, apoptosis has been identified in the rat model as a possible key event (though not the only event) in eyelid separation.\textsuperscript{24} At the molecular level, regulation of eyelid development requires a bidirectional mesenchyme–periderm interaction, which is regulated by several signaling pathways.\textsuperscript{21,25–28} To better understand the phenotypic logic behind congenital upper eyelid colobomas and CO/FS in particular, these signaling pathways and their effector genes should be further scrutinized in detail.

**CLASSIFICATION SCHEMAS**

In general, eyelid colobomas fall under the rubric of craniofacial clefting.\textsuperscript{29} In 1976, Tessier\textsuperscript{30} listed 15 facial cleft types categorized into 4 groups based purely on their anatomical location. Unfortunately, Tessier classification is strictly an anatomical classification, describes both soft tissue and bony clefts, is descriptive of the entire face and not just the eyelids, is absolutely lacking with regard to syndromic colobomas associated with systemic features, and most importantly is more commonly associated with lower eyelid colobomas than their upper eyelid counterparts. The authors attempting to classify upper eyelid colobomas have traditionally focused on CO/FS more than on GS and usually ignored simple colobomas (SCs) that belie any classification schema.\textsuperscript{29–35}

We can foresee in the not too distant future a categorization of upper eyelid colobomas based on genetic or molecular signatures of each particular anomaly, but until the unique genetic bases of these misleadingly similar phenotypes (FS versus GS versus nonsyndromic varieties) are completely understood, we will adopt a simple classification scheme solely for the purpose of the present discussion.

**I. Isolated coloboma**

A. Coloboma associated with CPA (CO)
   a. Complete
      i. No discernable eyelid differentiation, and the eyes are completely covered with skin
   b. Incomplete
      i. A skin fold devoid of tarsus covers the medial aspect of the palpebral aperture
      ii. Significant CPA
      iii. Lower fornix and lateral upper eyelids usually spared
   c. Abortive type/congenital symblepharon variant (CSV)
      i. True coloboma of variable sizes with a diverse range of CPA
      ii. Lower fornix and lateral upper eyelids usually spared

B. SC
   a. Upper eyelid coloboma in isolation not associated with CPA

**II. Syndromic variants**

A. FS
B. GS/oculoauriculovertebral spectrum (GS)
C. Rare syndromes
   a. Manitoba oculotrichoanal syndrome
   b. Ablepharon-macrostomia syndrome
   c. Nasoalpalpebral lipoma-coloboma syndrome
   d. Anomiotic band sequence
   e. Oculoectodermal syndrome
   f. Neurocutaneous syndromes
      i. Encephalocraniocutaneous lipomatosis
      ii. Dellemann syndrome or oculocephalocutaneous syndrome
      iii. Linear nevus sebaceous syndrome
   g. CHARGE syndrome

**ETIOLOGY AND PATHOGENESIS**

To this date, the network of genetic mutations responsible for upper eyelid colobomas is largely unknown, and possible environmental factors or mechanical events during pregnancy may contribute to the development.

**Isolated Coloboma**

*Coloboma Associated With Corneo palpebral Adhesions (CO).* Most cases of CO are sporadic with unknown etiology probably resulting from a de novo mutation,\textsuperscript{36} but familial cases have been reported,\textsuperscript{36–42} and a case could be made that CO is an arrested form of FS based on the fact that within some families with FS, there are family members with isolated CO.\textsuperscript{38}

Although Thomas et al.\textsuperscript{37} erroneously suggested that the familial cases of isolated CO are of dominant inheritance, it was recently argued that these cases follow an autosomal recessive pattern of inheritance.\textsuperscript{38} Another possibility is that CO is a disruption anomaly because 2 mothers in our case series were possibly exposed to a teratogen in early pregnancy: the first was accidentally exposed to x-ray irradiation with her elder son and the second was a nail technician with long-term exposure to nail glue and nail gels.

**Simple Coloboma.** Isolated SC without CPA and without any systemic features represent an enigma. Whether they are an arrested form of GS remains to be determined.

**Syndromic Variants**

*Fraser Syndrome.* An insight into genetics of FS has been greatly increased with the study of a certain family of mice mutants termed “bleb mice,” because the shared defect in both conditions is a profound loss of adhesion of epidermis to the underlying basement membrane that results in abnormal epidermal blistering in the mouse embryo.\textsuperscript{44} In normal mouse embryos, a group of closely related proteins called the FRAS/FREM protein family are universally present in all basement membranes throughout the body and contribute to embryonic epithelial–mesenchymal integrity and tight adhesions during embryogenesis.\textsuperscript{45–48} When this intricate process of epithelial–mesenchymal protein trafficking is interrupted by a genetic knockout either experimentally (*Fras1*\textsuperscript{−/−} mice), or in bleb mice, or in humans with a deficiency in chromosome 4q21 or 13q13.1, which encodes FRAS1 or FREM2, respectively,\textsuperscript{49} the most common resulting phenotype is composed of renal anomalies, abnormal fusion of the digits and the eyelids in addition to subcutaneous hemorrhagic blisters in mice. Mutations in either of these 2 autosomal recessive genes were demonstrated in 50% of patients with FS; however, other genes have been implicated recently.\textsuperscript{49–52}

As we shall see later, the phenotypic features of FS are extremely variable and pleiotropic, and several other distinct syndromes such as Manitoba oculotrichoanal syndrome and ablepharon-macrostomia syndrome may overlap FS and may suffer mutations in the FRAS/FREM complex.\textsuperscript{38,53–56}

*Goldenhar Syndrome.* Goldenhar syndrome is usually sporadic; however, familial instances have been demonstrated suggesting an autosomal dominant or autosomal recessive inheritance.\textsuperscript{37} Various chromosomal abnormalities have been found in GS such as trisomy 7, 9, or 22; mosaicisms; deletions...
at chromosome 18q or 22q; or unbalanced translocations between chromosomes 5 and 8.57–61 A long list of possible teratogenic factors causing GS includes smoking; cocaine use during pregnancy; diabetic embryopathy; primidone, retinoic acid, or thalidomide use during pregnancy; and an unknown toxin use during the Gulf war.62,63

EPIDEMIOLOGY

Isolated Coloboma

Coloboma Associated With Conorneal Aphebral Adhesions (CO). In their comprehensive review in 1986, Thomas et al.37 reported a total of 27 patients with isolated CO with equal sex distribution of whom 16 were sporadic and 11 were familial. A history of consanguinity was demonstrated in 12.5% of patients. A close examination of the 27 nonsyndromic cases recorded by Thomas et al. shows that they were in error because the same 3 family members published by Coover39-41 in 3 separate articles apparently belong to the same family presented by Magruder62 10 years later bringing the actual number to 24. A major review article published in 2002 mentions an additional 29 cases.38 Several additional reports have appeared in the literature afterward,66,67,69,70,71,72 and a review of our own medical records revealed 17 patients with isolated CO without any systemic findings. The exact number of nonsyndromic CO patients reported in the literature is difficult to determine because unfortunately 2 major reviews in the literature focused on FS alone and disregarded isolated CO.65,66 and the largest 3 published case series in the ophthalmic literature made no attempt to differentiate isolated CO from syndromic cases.4,32,33

Simple Coloboma. To the best of our knowledge, no epidemiologic data are available. Reports of SCs without CPA are sparse, and a literature review would give the erroneous impression that CO is more prevalent, which is merely an error in reporting because the striking features of CO make it more palatable for publishing. Nouby11 reported 5 patients with SC, while another article reported an additional 15.12 The superior fornix is vaguely referred to in the latter article as “adequate,” and it is not clear whether the superior fornix in these 15 patients was completely free or not because in our experience, patients with CO may have a variable yet constant degree of CPA, which may be minimally visible on casual observation. In our own practice, we have only encountered 2 patients with SC without CPA or any systemic defining features.

Syndromic Variants

Fraser Syndrome. Fraser syndrome is a very rare syndrome with fewer than 300 cases described in the literature so far.65 It has an estimated prevalence that varies between 0.20 and 0.43 per 100,000 liveborn infants.64,65 Because of the potentially life-threatening respiratory defects of FS, the reported incidence among stillbirths is higher, 11.06 per 100,000.65 Reported rates of consanguineous marriages varied from 15% to 49%,37,38,65 and reported gender differences are also variable. A recent European study has demonstrated considerable heterogeneity in prevalence rates depending on geographic distribution.37,38,65 In our own case series, 3 out of 5 patients with FS were descendants of the same geographic location in Egypt (Upper Egypt) where consanguineous marriage is the rule.

Goldenhar Syndrome. Epidemiologic data are sparse and inconsistent with estimates ranging from 1/3,500 to 3.8/100,000 live births. The best guess is around 1/5,600 live births.8,70

CLINICAL PICTURE

Isolated Colobomas

Colobomas Associated With Conorneal Aphebral Adhesions. The clinical features of CO vary from a SC with minimal CPA to a truly “hidden” eye or complete CO. We usually find it hardly convincing to categorically embrace François31 subclassification of cases with CO into complete CO (cryptophthalmic typique), incomplete CO (formes incompletes, atypiique, or partielles), and CSV (formes abortive), all of which may coexist in both eyes of the same patient (Figs. 2A and 3B) or in siblings.71 We believe that the clinical spectrum of CO represents a continuum probably resulting from the same genetic defect; however, for the purpose of the current discussion, we still tried to distinguish the various clinical types, although we agree with Gupta and Sen37 that CO may not uniformly lend itself to a rigid clinical classification schema at least until the genetic bases are well defined.

Complete CO. In these patients, the forehead skin extends over the globe and onto the cheek without any discernable differentiation of eyelids except occasionally where a dimple or scar is seen at the site of presumed fusion of both eyelids although as we will discuss later, this dimpling is associated with a different phenotype of CO.6,73

The ocular structures in complete CO are usually atrophic and grossly disorganized, but the eye may be normal in size or even enlarged, may occasionally present as a cyst (Fig. 1D),33,36,73,74 and may occasionally express a reaction to light.71

The extraocular muscles may be of normal size for age or may be ill defined, with limited ocular motility, which could be seen and felt with palpation.31,74 The globe may be central, but may be displaced horizontally or vertically (Fig. 1A–C).

The eyebrows are seldom normally developed,66 and more commonly the entire eyebrow, its medial 2/3 or its lateral 1/3, is absent.72,74 A tongue of hair, which is not yet quite distinct at birth, may be seen extending from the scalp hair into the lateral 1/3 of the eyebrow.72,74 In our experience, alopæcia of the eyebrows may occur anywhere and may not follow a specific pattern (Figs. 1–4).

In complete CO, the conjunctiva is wholly absent and the skin is completely adherent to the anterior surface of sclera and cornea by fibrous tissue. The condition may be unilateral or bilateral.71

Histopathologically, the eyelids are replaced by undifferentiated fibrous tissue, with total absence of the tarsus, meibomian glands, cilia, and lacrimal glands,31,33,74 but the orbicularis oculi and the levator muscles are usually preserved, and the extraocular muscles may be present or absent.31 The conjunctiva is usually absent in histologic sections, and the cornea is usually replaced with “intertwining collagen bundles” with no epithelial or endothelial lining.31,74 While the anterior segment might be malformed, the choroid, retina, and optic nerves appear to be normally formed.74

There appears to be a distinct form of familial (autosomal dominant), bilateral isolated CO that was reported only 3 times in the literature called autosomal dominant CO.36–38 The palpebral features are quite distinct from typical complete CO in that the eyebrows are completely normal and the eyelids appear grossly as if they have normally developed, but later fused together and to the globe. Additionally, these patients usually have Peters anomaly, a feature not documented in classic complete CO (Fig. 6D).36

Incomplete CO. A subset of CO patients has an ill-defined upper eyelid or an incomplete skin fold devoid of tarsus covering almost the entire cornea. This fold is completely fused to the underlying keratinized cornea along the entire length and width of the fold, and may or may not extend downward to fuse with the lower eyelid. This abnormal fold does not cover the
entire eye; hence, there is the partial or incomplete designation in François clinical observations. These patients usually have an insignificant upper eyelid coloboma because the colobomatous part of the eyelid is partly replaced by the skin fold (Fig. 2A,B).

In his original description of incomplete CO, François describes a rudimentary presence of the lateral eyelid structures and conjunctival fornix, which is almost a constant feature in incomplete CO and in CSV even in its most severe forms, and contrary to previous authors who maintained that no normal eyelid tissue could be observed medial to the coloboma, we of this series have observed 1 patient in whom a small lip of normal rudimentary upper eyelid was present nasally together with a functioning upper punctum and canaliculus (Fig. 2B). The inferior fornix may or may not be spared depending on the inferior extent of the abnormal skin fold (Fig. 1C). Contrary to François’ description that patients with “incomplete CO” have microphthalmic eyes, we have encountered patients with incomplete CO whose eyes are of normal size echographically. Of the 3 subtypes of nonsyndromic CO in François classification, incomplete or partial CO is the rarest.

In all, 2 of the 3 patients with incomplete CO in our series were strictly unilateral, and the third patient only had an insignificant notch with minimal CPA in the contralateral upper eyelid.

Congenital symblepharon variant. In CSV (also referred to as abortive CO or partial CO), the upper eyelid skin is deficient and the remnants of it are visibly adherent to the globe, hence the designation “congenital symblepharon.” The lower eyelid is usually spared, and corneal involvement depends on the extent and severity of CPA. Subramanian and associates classified CSV into mild, moderate, and severe grades based on the extent of the coloboma and the severity of CPA. In our experience, the defect may indeed range from a minor notch in the eyelid margin associated with minimal CPA overlying the coloboma or even adhesions confined to the limbus in patients in whom there is a near-total eyelid colobomatous defect with extensive involvement of the cornea (Figs. 3A–D).

The term CSV is actually a relic of late nineteenth century medicine, and should be abandoned as it may erroneously imply that in the other 2 varieties (complete and incomplete CO), the cornea is spared or is at least less affected than in CSV while the opposite is actually true as the extent of CPA (which is a universal finding in all 3 types without which the diagnosis of CO should be called into question) is in fact less in CSV than in complete or incomplete CO where the conjunctival sac may be entirely absent.

FIG. 1. Complete cryptophthalmos. Various clinical presentations of complete cryptophthalmos. A, Typical complete cryptophthalmos with total absence of the eyelids, eyebrow, eyebrow hairs, and a centrally located normal sized globe. B, A medially displaced globe with total absence of the eyebrow and eyebrow hairs except laterally. A skin tag is seen lateral to the globe. Note ipsilateral absence of the nasal cavity. C, A failed previous reconstruction attempt in a patient with complete cryptophthalmos showing an enlarged proptotic centrally located globe with total absence of the eyebrow ipsilateral to the defect and a contralateral tongue of hair replacing the eyebrow—underlies the difficulty in managing these patients. A previous cleft lip repair is also seen ipsilateral to the cryptophthalmic eye. Note the contralateral microphthalmic globe. D, CT scan of the same patient showing the globe replaced by a figure-of-eight cystic lesion to which normally sized extraocular muscles are attached posteriorly. Note the widening of the superior orbital fissure and the defect in the greater wing of the sphenoid. (*) This globe did not react to light shown through the skin in contrast to the contralateral microphthalmic globe that showed some reaction to light.

FIG. 2. Incomplete cryptophthalmos. Various clinical presentations of incomplete cryptophthalmos. A, Abnormal skin fold in the medial part of the upper eyelid adhering to the underlying cornea. Normal eyelids remnants could be seen lateral (A,B) and medial to the skin fold, and the upper punctum was also preserved (B). In both examples, the eye is quite, with a small coloboma and minimal keratopathy. Note the bifid nose ipsilateral to the defect in A. The other eye of the patient in A is in Figure 3A. C, A more severe case with the skin fold extending to and fusing with the lower eyelid. The medial part of the upper and lower eyelids are abnormal and no puncti are present, but the lateral part of the eyelid is preserved. D, Surgical division of the eyelid fold clearly illustrates the cornea showing through the thin skin fold, which is completely devoid of tarsus (**) in contrast to the normal lateral part of the eyelid where the tarsus is preserved (short arrow). Also, check Figure 1B in Tawfik.
Although Nouby maintains that these colobomatous defects assume a triangular shape in contrast to the typically quadrangular shape of SCs and colobomas associated with GS, we consider it a futile exercise to try to ascribe a certain shape to these colobomas. They could indeed appear triangular if minimal in size (Fig. 3A), but they assume a relatively quadrangular shape as they grow larger (Fig. 3B), and it is more accurate to describe CO colobomas as “irregular” in shape because the extent of the typically variable CP A governs the final shape of the defect (Fig. 3C,D).

**Simple Coloboma.** According to Mustardé, these “pure colobomas” are strictly unilateral, have no associated systemic findings, do not usually present with significant keratopathy despite the corneal exposure, and the upper fornix is always well formed with normal depth. The shape of these colobomas is typically quadrangular, but we agree with Van Der Meulen that it may also assume a triangular configuration, and for reasons unknown, they are almost exclusively confined to the junction of the medial and central parts of the eyelid. The actual size of the defect is difficult to ascertain because the edges are pulled in opposite directions by the separated parts of the orbicularis muscle, which is apparently contracting freely because the eyelids in these patients are not tethered to the globe in any way. This fact may explain why corneal exposure may be less pronounced than would be expected even with a big eyelid defect.

**Syndromic Variants**

**Fraser Syndrome.** In 1962, George Fraser first described the syndrome bearing his name, and in more recent times, several excellent reviews have appeared in the literature, where criteria for diagnosing FS were established and its extensive clinical variability was demonstrated. In 1986, Thomas et al. framed the diagnostic criteria for FS. They defined 4 major criteria and 8 minor criteria, and suggested that the diagnosis should be made with 2 major and 1 minor criteria, or 1 major and 4 minor criteria. In 2007, van Haelst et al. suggested that FS is better defined if 3 major criteria are confirmed. Complete CO is the subtype most
commonly associated with FS, and CSV is the least. A tongue of hair extending from the temple to the eyebrow (Fig. 4F) is encountered in around 35% of FS patients and is considered by some authors to be a minor feature of FS. We occasionally observe the same finding in patients with isolated CO, and we do not believe it is specific to FS, as this abnormality is simply considered a general indicator of maldevelopment of the upper eyelid region because normal eyelid development suppresses hair growth in the forehead.

The most common major nonocular criterion of FS is cutaneous syndactyly of the hands and feet, which usually involves fusion of the second, third, and fourth digits with a reported frequency that varies between 62% and 95%, followed by ambiguous genitalia (40%–66%), urinary tract abnormalities are also quite common (37%–80%), and usually take the form of unilateral or bilateral renal agenesis, renal hypoplasia, ureteral agenesis, or less common bladder abnormalities. A positive family history (40%–60%) of the disease is also an important requisite for diagnosing FS. Respiratory tract abnormalities in the form of laryngeal and/or tracheal stenosis are very frequent findings and are currently considered as one of the major features of FS, and should be considered when FS patients are subjected to general anesthesia.

Minor features are not infrequent (Fig. 4) and include congenital malformations of the ears, which are found in up to 75% of patients with FS patients (low set, malformed, posteriorly rotated, or dysplastic); nasal malformations (~50%), which take the form of a wide nasal bridge, an absent or hypoplastic nasal ala, or a bifid nose; cleft lip/palate; skeletal abnormalities, which may manifest in the skull, ribs, or limbs (Fig. 4C, E); and umbilical anomalies. Rarer features include craniofacial malformations, mental retardation, and congenital cardiac malformations. The prognosis for life is generally poor. Almost half of FS patients will not survive beyond the first year of life, and only 2% make it beyond the age of 20 years.

Goldenhar Syndrome. With a causally heterogeneous etiology and with such a wide variability of expression, it comes as no surprise that GS bears 16 different names in the literature, which until recently were thought to represent separate entities. Goldenhar syndrome is a pleiotropic condition with a spectrum of cardiac, renal, and skeletal manifestations besides the typical facial and vertebral anomalies. Therefore, the term oculoauriculovertebral spectrum was suggested to be better descriptive of the spectrum of anomalies in GS because names such as hemifacial microsomia and first branchial arch syndrome give the erroneous impression that GS abnormalities are limited to the face only.

There are several conflicting classification schemes and no general consensus on criteria for diagnosis. Strömland et al. proposed that to establish the diagnosis, 2 of the 4 major criteria they suggested have to be met (orocraniofacial, ocular, auricular, and vertebral), but Tasse et al. excluded ocular manifestations from the major criteria of GS on statistical bases.

As a syndrome with such diverse clinical features and conflicting reports of laterality and sex predilection, it is interesting to note that there exists a mandatory feature of the syndrome that is microtia and/or preauricular tags (composed of skin and cartilage), which are present in 95%–100% of patients and may be bilateral in up to half of the patients even if other manifestations are strictly unilateral. In familial cases, the diagnosis is considered even if preauricular tags are the only manifestation of the disease.

Flattening of one half of the face causing marked facial asymmetry (hemifacial microsomia) is quite common and second only to ear anomalies and is caused by an underdeveloped mandible, maxilla, or zygomatic bone with partial atrophy of the muscles of expression and muscles of mastication. Cervical spine abnormalities are the third most common feature of GS, but minor manifestations also occur frequently, and some of them may tend to cluster together. These include deafness, facial clefting, facial nerve paralysis, urogenital anomalies, brain anomalies, congenital heart defects, delayed motor development, short stature, delayed speech development, and microcephaly.

The hallmark of ocular features in GS is an eccentric or limbal epibulbar dermoid (ED), the presence of which should prompt the clinician to look for other ocular anomalies as they are positively correlated with the presence of ED. The most common location is inferotemporal, but nasal limbal choristomas have been reported.

Strikingly more yellowish than ED (because of a substantial deep layer of mature fat cells), lipodermoids (dermolipomas) tend to be less frequently associated with GS than ED and are not only limited to the superotemporal quadrant but may also occur inferiorly (Fig. 5A). The true prevalence of both is unknown as ED and lipodermoids are usually grouped together in cohort studies in the nonophthalmic literature, but the percentage varies from 12% to 100%.

Dermolipomas and ED are more commonly associated with GS than upper eyelid colobomas, the frequency of which tend to increase with increasing severity of GS. The reported frequency of upper eyelid colobomas ranges from 6% to 24%, 37,84,91,92 Usually unilateral and occasionally bilateral, the most frequent location for these colobomas is at the junction between the medial and central thirds of the upper eyelid. Although Fries and Katowitz mentioned the lower eyelid as a possible location for eyelid colobomas in GS, we believe that the local distribution of the coloboma (junction of medial and central thirds of the eyelid), coupled with the fact that it may even occur in the other eye, in addition to our own observation of the association of small EDs with large upper eyelid colobomas, all belie this hypothesis. By definition, the upper fornix is deep and well formed and these colobomas are not usually attached to the surface of the eye, but a small pedicle may occasionally connect the coloboma to an exceptionally large ED (Fig. 5B).

Although some authors mention the lower eyelid as a possible location for eyelid colobomas in GS, we believe that what they observed is actually a shallow, wide depression rather than a true coloboma caused perhaps by mechanical pressure of the ED on the lower eyelid during development rather than a true coloboma.

Additional ocular features include ptosis (12%), nasolacrimal abnormalities (11%), horizontal phimosis, and strabismus (10%–19%) in the form of esotropia, exotropia, or Duane syndrome. Microphthalmia and anophthalmia can occur with a reported frequency equal to or even exceeding that of upper eyelid coloboma. Rarer associations include eyelid skin tags, iris coloboma, tortuous retinal vessels, choroidal colobomas, hypoplastic optic nerve, macular hypoplasia, and a tilted optic disc. Unfortunately 3 of the 4 major articles dealing exclusively with
the ocular features of GS date back to the seventies and mid-eighties, and the fourth focuses on dermolipoma only.88,89,92,95 A fresh insight into the ocular findings of GS in a pediatrics setting and not in an ophthalmic referral center (where referral bias may skew the results) is warranted.

RARE SYNDROMIC ASSOCIATIONS WITH CONGENITAL UPPER EYELID COLOBOMA

A detailed discussion of the syndromic curiosities associated with upper eyelid coloboma, including Manitoba oculotrichoanal syndrome,ablepharon-macrostomia syndrome, amniotic band sequence, oculoectodermal syndrome, and neurocutaneous syndrome, is beyond the scope of the current discussion and is reviewed elsewhere.34,53–56,96–127 The distinct facial and ocular features of some of these syndromes are outlined in Figure 6.

MANAGEMENT

Upper eyelid coloboma may represent one of the few oculoplastic emergencies that may be faced at a very early age. Operating on very young infants with multiple congenital anomalies,37,38,68 with attendant possible anesthetic risks,81,82 dealing with the shocked and grieved parents of a “blind” or a “disfigured” child, coupled with the relative lack of tissue for reconstruction could be a major surgical challenge.34,82 Families should be counseled that several operations may be required, and in cases of CO/FS the visual potential may be poor despite multiple surgeries, and that even in the absence of good visual outcome, cosmetic rehabilitation might not be perfect.128

In discordance with the rest of the text, the management of CO/FS colobomas will be discussed together with the management of SC/GS because the basic management principles are similar. Therefore, we will split the management into 2 sections according to the presence or absence of CPA.

Although several shared reconstruction techniques are employed in either category, they will be dealt with separately. Rather than giving a detailed discussion of the various methods of upper eyelid reconstruction, which is well beyond the realm of this text, we will focus on relevant surgical points that are pertinent to the discussion.

Colobomas Not Associated With CPA (SC/GS). For small colobomas without keratopathy where the defect size could
be overrated because of the unrestricted pull of the orbicularis muscle, several authors recommend watchful observation, deferring management till the ripe age of 2 to 4 years when the eyelids have grown to a more manageable size and more tissue is available for reconstruction, particularly if they have a good Bell phenomenon.29,76,129

For small defects that do require suturing (up to 25%), direct closure may suffice, although for moderately sized defects (25%–50%), where a severing of the upper crus of the lateral canthal tendon is required for satisfactory closure. We do not recommend direct closure even if clinical judgment intraoperatively favors a simpler direct closure approach. This is primarily because the upper crus readily readheres by scar tissue,29 and this could result in early wound dehiscence despite the fact that it was sutured without any undue tension on the edges.130 Therefore, in the context of congenital upper eyelid coloboma, caution is warranted in relying too heavily on the often quoted dictum that when defect edges are brought under “normal” tension, the “real” size of the defect is actually smaller than it appears.129,131 because it overlooks the relative lack of underlying laxity in infants.130 Even if early wound dehiscence does not occur after direct approximation, severe ptosis is observed that may persist for several months29 obstructing the visual axis, which is potentially amblyogenic and may exacerbate the ptosis. What further complicates the picture and exacerbates the ptosis is that with direct closure, it is not usually possible to resuture the levator muscle and counter the ptosis for larger defects (50% or more of the eyelid), available options include the Cutler-Beard procedure, an eyelid rotational (switch) flap, or a tarsomarginal graft. The classic or still better “modified bridge flap,” where a spacer graft is used beneath the flap, provides excellent donor–recipient match but has several disadvantages; it is potentially amblyogenic, which is of real concern in SC/GS where the visual potential is good. Lower eyelid instability and inferior fornix shortening are also of particular concern because they assume that there is an excess of lower fornix conjunctiva while in fact there is not. Postoperative lower eyelid retraction is a real concern. Another concern raised by parents postoperatively is bulkiness of the bridge flap, which tends to persist and does not improve with time, and may require revision prior to school age. An often overlooked source for posterior lamellar reconstruction if a modified bridge flap is chosen in cases of GS is the cartilage in the preauricular skin tags,128 which is composed of keratinizing epithelium surrounding a central core of elastic cartilage,148 and is occasionally large enough to provide sufficient cartilage for posterior lamellar support.

An issue frequently raised by cosmetically concerned parents when the Cutler-Beard procedure is suggested is the lack of eyelashes in the reconstructed area, and for this reason, an eyelid switch or rotational flap may provide a better cosmetic outcome than a bridge flap.32,78,135,137 After careful fashioning of a medi ally based or a laterally based full thickness eyelid switch or rotational flap on an adequate (5–6 mm) vascular pedicle incorporating the marginal arcade,29 the flap is rotated 180°, secured in a lamellar fashion to the freshened edges of the remnants of the colobomatous eyelid, and is used to fashion a new upper eyelid margin, which is separated 2 to 3 weeks later. Up to 50% of the upper eyelid can be reconstructed with only 25% of the lower eyelid, and the defect in the lower eyelid is easily closed directly although occasionally a rotational check flap may be required.4,29,78,135,136

Another option in patients with SC/GS is the use of a tarsomarginal graft covered with an overlying skin-muscle advancement flap, which does not occlude the pupil and may be a better option than a eyelid sharing procedure.131 It is a single-stage procedure that is less demanding in terms of blood supply requirements than a full-thickness composite eyelid graft because it receives additional blood supply from the overlying skin-muscle flap. However, parents are occasionally concerned about harvesting tissue from the contralateral normal side, and therefore, the ipsilateral lower eyelid may be chosen.137 If taken from the contralateral side, it is recommended that to get a good contour, temporal defects should be reconstructed with grafts taken from the nasal eyelid and vice versa.131

Colobomas Associated With CPA (CO/FS). The management of colobomas associated with CPA (CO/FS) differs from SC/GS in several respects, particularly in the fact that in the latter, no reconstruction of the fornix is required, while in CO/FS, a separate or combined 2-stage reconstruction is usually required. Another valid clinical point to remember is that in contrast to SC/GS where it is not always easy to define the exact size of the defect,29 the size of the defect in CO/FS observed clinically is more accurate because the CPA fix the defect in place and limit the freedom of motility of the orbicularis ocu- lus muscle. In either case, any form of measurement will be largely inaccurate, but as a rough estimate, Mustarde recommends counting and comparing the number of eyelashes in both eyelids.

It should be remembered that prior to eyelid fusion, the corneal epithelium is fused with the surface ectoderm, and only after eyelid fusion, do they separate and the cornea takes its normal developmental course. Consequently, by definition, a “patient with CO will not have a normal cornea.”4 This dictum is not absolute and in our experience, when this “abnormal cornea” causes adhesions to recur after surgical reconstruction of the fornix, they tend to occur in exactly the same area where they were initially observed and they had a tendency to spare the originally “normal” part of the cornea. Thus, it may be better to rephrase by saying that a patient with CO will not have a normal cornea in the area corresponding to the CPA. Accordingly, parents should be informed that complete and incomplete COs are incompatible with normal vision, and the visual potential in CSV is dependent on the extent of adhesions at the first presentation.

Complete CO. Complete CO deserves a special category of its own because technically there is no coloboma, the eye is painless with no risk of impending perforation, and as we mentioned earlier, normal development of the cornea is impossible in the first place and fornix reconstruction for prosthetic shell placement is extremely challenging because the surgeon has the double task of creating a fornix and recreating the eyelids.159 Therefore, Saleh et al.16 preferred deferring these surgeries on the grounds of poor visual, cosmetic, and reconstructive outcomes, and they got disappointing results when forced to operate by the parents on psychological grounds. If surgery is to be undertaken, the surgeon should be performed in a stepwise fashion and the first objective is the elusive task of creating a conjunctival sac.4,7 The skin covering the ocular remnants is divided followed by placement of a conformer covered with a mucus membrane (MM) graft. Eyelid reconstruction with stiffening of the posterior lamella and possibly further socket MM grafting could be carried out 1 year later.4 An alternative source for socket reconstruction if MM grafting fails in these difficult cases is the preputial skin in uncircumcised children.139,140

In patients with complete CO, orbitalpalmpebral cysts are infrequently observed and probably represent a surface ectodermal anomaly rather than a true ocular cyst caused by failure of invagination of the primary optic cup.40,141 These cysts pose a controversial
described by Witmer and Slonim who used a lateral modification could be attempted. An innovative technique was recently a challenging problem, and a Tenzel flap or direct approximation the abnormal skin fold extends to the lower eyelid may pose the contents at least at an early age could lead to underdevelopment of the bony orbit with subsequent facial asymmetry. In our own case series, we encountered a single FS patient with a unilateral orbitopalpebral cyst after a previous failed attempt at surgical reconstruction elsewhere, and it did not react to light although the contralateral microphthalmic eye did (Fig. 1C,D).

**Incomplete CO.** Incomplete CO sometimes poses a challenging problem in trying to explain to the parents why a poor visual potential is expected. To the parents’ eyes, it may look less devastating than either complete CO or CSV because the coloboma looks small as it is fictitiously reduced in size by the skin fold, the diseased part of the cornea is completely concealed, keratopathy is unusual, the eye is painless, and the remaining exposed part of the cornea usually looks normal (Fig. 2). Saleh et al. caution against rushing to early surgery, because most of the cornea is keratinized and the prognosis for functional or cosmetic reconstruction is dismal at best. We tend to agree that incomplete CO does not pose a surgical emergency except if parents are devastated by the disfigurement, and in that case, surgery may be necessary on cosmetic bases alone because in our experience, recurrence of adhesions after fornix reconstruction is the rule rather than the exception.

If reconstruction is to be undertaken, an eyelid sharing procedure or an eyelid switch procedure should be used. After severing the CPA, and excision of the abnormal skin fold, the defect is usually more than 50% of the eyelid and would not lend itself to direct approximation. The use of a switch or a bridge flap might actually reduce the recurrence of adhesions, because by transposing “normal” tissue, including palpebral conjunctiva from the normal inferior fornix to its narrow superior counterpart, the upper eyelid and palpebral apertures are widened superiorly. Patients with incomplete CO where the abnormal skin fold extends to the lower eyelid may pose a challenging problem, and a Tenzel flap or direct approximation could be attempted. An innovative technique was recently described by Witner and Slonim who used a lateral modified sliding Hughes procedure where a tarsococonjunctival flap is fashioned from the lateral part of the same eyelid, which usually has a substantial and normal tarsal remnant to work with (Fig. 2D). This flap is advanced horizontally and secured to the medial canthal tendon and medial edge of the eyelid, followed by placement of an overlying skin graft. A possible source for skin grafting is the excised skin fold, which covered the cornea.

With the possible failure of salvaging vision in these eyes and with future prosthetic placement in mind, every attempt should be undertaken at reconstructing the superior fornix even if the visual potential is poor. Significant controversies exist in the literature regarding the timing and type of the graft used for fornix reconstruction. There is no clear consensus whether fornix reconstruction should be carried out concomitantly with eyelid reconstruction or deferred until flap separation and opinions are split between both approaches. Our personal preference is to defer fornix reconstruction to be performed with flap separation because as we mentioned earlier, a switch flap might actually help deepen the fornix by lengthening the eyelid. If such an approach is chosen, the distal end of the severed conjunctiva in the first procedure is sutured in a back fashion with a double-armed 6-0 polyglactin suture to the superior fornix, which is exteriorized and sutured on the skin before the levator muscle is sutured to the tarsus, followed by fornix reconstruction at a later stage.

The second controversial issue is the type of graft used. While some authors have excellent experience with amniotic membrane (AM) grafting, others argue that the AM has a tendency to dry out and contract and is not recommended in CO/FS. It should be noted that AM grafts are substrate grafts not substitute grafts and require a substantial source of conjunctival holoclones to grow on the surface of the AM, a situation which may be difficult to meet in CO/FS. We have experienced inconsistent results with both AM and MM grafts, and regardless of the type of the graft, CPA may recur in the same area where it was located originally. Therefore, we conclude that the rate limiting step in fornix reconstruction in CO/FS patients is the extent of CPA initially observed before surgical intervention rather than the type or timing of the graft.

**Congenital Symblepharon Variant.** Upper eyelid colobomas in this variety are potentially vision threatening and should be promptly treated. In our country and in Europe, CO/FS has a predilection to occur in distant geographic locations where close follow up is impossible. Consequently, watchful observation cannot be advocated except in eyes with minimal colobomatous notches and in the absence of keratopathy (Fig. 3A).

The same basic management principles as in incomplete CO apply, and except when the defect is really small where direct suturing could work, we generally favor an eyelid switch flap technique or an eyelid sharing procedure. In our experience, recurrence of CPA occurs more frequently when direct suturing is undertaken. The cause of this is unknown, but it could be theorized that when an eyelid sharing procedure is employed, the area of the cornea that was adherent to the eyelid remnant is no longer in contact with the diseased upper eyelid but rather faces an overlying normal conjunctiva and tarsus from the unaffected lower eyelid, an effect that is further exacerbated if the remnants of the levator muscle are sutured to the edges of the rotated tarsus, thus lifting the abnormal eyelid remnants/ flap further away from the damaged area of the cornea.

Obviously, a contralateral tarsomarginal graft is not an option in bilateral cases, and it should not be used even when the other eye is minimally affected, so as not to compromise the visual potential of the “normal” eye. When an AM is used for reconstruction (AmnioGraft, Bio-Tissue, Miami, FL, U.S.A.), a 1.5 cm × 1 cm graft is sufficient to cover the entire fornix and the affected part of the cornea after careful superficial keratectomy, although in patients with incomplete CO a 2.5 cm × 2 cm piece is preferable as the defect is larger. The graft is secured with fibrin glue (Fibroglo, CMCCB, Cairo, Egypt) and not with sutures to reduce irritation and postoperative inflammation, followed by placement of a specially designed symblepharon ring with 2 adjacent superior holes. A double-armed 6-0 polyglaclin suture is passed through these holes and the superior fornix, and then advanced full thickness through the upper eyelid to be sutured directly on the surface of the skin without using bolsters.

When an MM is used, it should be thinned as much as possible to ensure a good take. To avoid suture irritation and in an attempt to minimize any possible source of postoperative inflammation, we also fix the MM graft in place with fibrin glue followed by placement of a symblepharon ring. In our hands, recurrence of adhesions is observed frequently although the casual observer would get the calming impression that the fornix looks significantly deeper, which is simply due to eyelid lengthening from the lower eyelid. This is of paramount importance if a penetrating keratoplasty is planned, and should be pointed out to the cornea surgeon very clearly, because even if the future cornea would seem to receive proper protection from the reconstructed eyelid, when this eyelid is carefully lifted off the globe, the adhesions may still be located in the same exact place where they were initially observed.
CONCLUSION

In the near future, advances in molecular genetic testing will help redefine the etiopathogenesis and the diverse clinical spectrum of genetic diseases associated with upper eyelid colobomas and will undoubtedly unravel the diagnostic dilemmas and phenotypic overlap that we have discussed in this review. It would also help families with afflicted individuals make better family planning decisions and may even offer gene therapy obviating the need of the oft frustrating surgical approaches. We sincerely hope that in a decade or less, this review article will be obsolete.

METHODS OF LITERATURE SEARCH

English and world medical literatures were searched from 1880 up through May 2014 using Google search and PubMed for papers staring from 1950 till the present, and for earlier papers, we used the Index-Catalogue (Library of the Surgeon-General’s Office 1880–1961) that could be accessed at http://indexcat.nlm.nih.gov/vivisimo/cgi-bin/query-meta?v:project=indexcat&v:sourcex=indexcat&sortby=ID. We used the following keywords: upper eyelid coloboma, colobomata, Fraser syndrome, cryptophthalmos, cryptophthalmia, Goldenhar syndrome, ocu.
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