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Brief report

Serious corneal complications and undiagnosed floppy eyelid syndrome; A case series and a 10-year retrospective review

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Abstract

Purpose: To describe three individuals with severe keratitis and a substantial delay before floppy associated eyelid syndrome (FES) was identified, and to estimate the prevalence of severe corneal disease in individuals with FES.
Methods: We defined severe keratitis as corneal ulceration, vascularization or scar that affected vision. We recorded the clinical characteristics, the duration of symptoms before the diagnosis of FES, subsequent management and outcome. Then, to determine the proportion of individuals with FES who had severe corneal disease, we interrogated the Moorfields Eye Hospital electronic patient record (EPR) for the diagnosis of FES made in the ten-year interval from 2008.
Results: Three individuals presented with severe progressive keratitis (median duration of symptoms 19 months, range 2–48 months). All were male and with a high body mass index (BMI, range 38.9–41.2). In each the etiology of the keratitis was unclear before FES was identified. All had very lax lids and were aware they had periods of lid malposition during sleep. None mentioned symptoms of obstructive sleep apnoea (OSA) until they or their partner were directly questioned. The management of keratitis included both medical and surgical corneal treatments, with tarsorrhaphy and lid shortening surgery. We identified an additional 104 cases of FES from the EPR, of which 4 (3.8%) had severe keratitis.
Conclusions: FES can be missed unless signs of lid laxity are directly elicited. A delay in diagnosis can result in clinical deterioration, with unnecessary investigations and treatments. An assessment for FES should be included as part of the evaluation of individuals with severe or chronic keratitis.

Keywords: Floppy eyelid syndrome; Corneal complications; Keratitis

Introduction

Floppy eyelid syndrome (FES) is a disorder characterized by extremely lax upper lids that can be everted by external skin traction, loss of tarsal plate rigidity and an upper tarsal papillary conjunctivitis.[1] In affected individuals, sleeping face down into a pillow can result in upper lid eversion and mechanical trauma to the conjunctiva or cornea, with secondary signs of chronic ocular surface irritation. Symptoms of chronic redness, stickiness and irritation are the usual reason for ophthalmic referral. Sight threatening corneal disease is rare, but associations include keratoconus,[2,3] corneal vascularization, microbial keratitis, and corneal perforation.[3,4] Affected individuals are typically overweight males, and there is a strong association with obstructive sleep apnoea (OSA).[5] Obese individuals may also have hypertension or diabetes.

The lid laxity of FES may not be evident unless it is directly elicited, and individuals may not be aware they have OSA. Failure to consider FES as a cause for chronic conjunctivitis or keratitis can lead to an unnecessary delay in starting appropriate management. Significant delays in

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diagnosis of FES are common, with a previous cohort of over 100 patients having a median time to diagnosis of 17 months, and range of up to 16 years, from the onset of symptoms.[6] The purpose of this paper is to describe three individuals who had severe progressive keratitis for a substantial period before the presence of FES was suspected. All three also had symptoms of OSA. To estimate the prevalence of severe corneal complications in individuals with FES we reviewed the clinical records of all individuals with a diagnosis of FES seen at this hospital over the ten-year interval from 2008.

Methods

The local research ethics committee approved this study, and it adhered to the tenets of the Declaration of Helsinki. For each individual we recorded the duration of symptoms, the features of their ocular disease, the subsequent management and the body mass index (BMI >25 = obese). The Moorfields Eye Hospital electronic patient record (EPR) was used to identify individuals potentially affected with FES seen in the 10-year interval from January 2008. We reviewed these records to confirm the diagnosis of FES and recorded the corneal signs, recalling the paper records if there was diagnostic uncertainty. Serious corneal disease was defined as corneal ulceration, vascularization or scar that affected vision. Affected individuals were not routinely examined for keratoconus or endothelial disease.[3]

Results

Case 1

A 37-year-old man with a BMI of 41.2 who had a 6-month history of bilateral conjunctivitis, worse in the left eye, treated with multiple courses of topical antibiotic. He then developed an acute secondary bacterial keratitis, from which coagulase-negative staphylococcus was isolated, and this was treated with topical vancomycin and ceftazidime. Despite one month of this treatment the ulceration progressed, and the cornea perforated. Following referral to our institution, he was diagnosed with FES with symptoms of OSA. An 8.50 mm penetrating keratoplasty was performed combined with a temporary lateral tarsorrhaphy. Despite a subsequent lateral canthoplasty, and a further tarsorrhaphy, there was continued corneal exposure with continued severe ocular surface inflammation, and the graft failed (Table 1, Fig. 1A–C).

Case 2

A 43-year-old male with a BMI of 39.5 who presented with an 8-week history of superior corneal ulceration (Fig. 1D). The initial diagnosis was peripheral ulcerative keratitis and he received treatment with oral prednisolone 80 mg daily and a botulinum toxin (BTX) induced ptosis to protect the cornea. Investigation for autoimmune disease was negative (ACE, RhF, *anti*-CCP, ANCA, ANA, Hepatitis C). The cornea perforated and *Enterococcus faecalis* and a Staphylococcus sp were isolated. Following transfer for a further opinion, he was diagnosed with FES and a right tectonic lamellar keratoplasty was performed combined with a temporary lateral tarsorrhaphy. He was referred for symptoms of OSA and he has had a lateral canthoplasty.

Case 3

A 44-year-old man with a BMI of 38.9 was managed over four years for idiopathic bilateral inferonasal corneal scars, worse on the left side (Fig. 1E–F). The scar on the left cornea was partly vascularized and it rapidly recurred despite 5 attempts at surgical removal, combined on occasion with fine needle vessel diathermy, subconjunctival injection of bevacizumab 2.5 mg, and topical mitomycin C (MMC) 0.02% applied to the base of the lesion after excision. Histology of the primary excision specimen reported a hypertrophic vascularized scar. FES was identified four years after the onset of symptoms. He usually slept on his left side and his partner confirmed he had symptoms of OSA. He declined lid surgery and sleep studies but opted instead to attempt weight reduction and to use ointment and a protective shield over the left eye at night. The signs have remained stable over the subsequent 11 months.

Our retrospective review from the EPR identified 104 cases of FES who attended over a ten-year period (Table 2). This did not include the three individuals described above, who were identified subsequently. Only a minority had required corneal review. Of these 104 individuals there were only 4 (3.8%)

Table 1
Clinical details of three individuals with severe keratitis who had delayed diagnosis of floppy eyelid syndrome (FES).

Case	Gender/age	BMI	Diagnosis delay (months)[a]	Corneal features[b]	Corneal management	Lid management	Final BCVA
1	M/37	41.2	7	Central corneal ulcer with perforation	Tectonic keratoplasty	Lateral canthoplasty, secondary tarsorrhaphy x 2	HM
2	M/43	39.5	2	Peripheral corneal ulcer with perforation	Lamellar keratoplasty	BTX tarsorrhaphy, temporary tarsorrhaphy, lateral canthoplasty	HM
3	M/44	38.9	48	Vascularised hypertrophic scars	Superficial keratectomy x 5, Vessel diathermy, MMC 0.02%	Temporary tarsorrhaphy	6/36

BMI: Body mass index; BCVA: Best corrected visual acuity at last follow-up; HM: Hand movement; BTX: Botulinum toxin; MMC: Mitomycin C.
[a] From onset of symptoms to diagnosis of floppy eye syndrome.
[b] There were no signs of keratoconus in either eye.

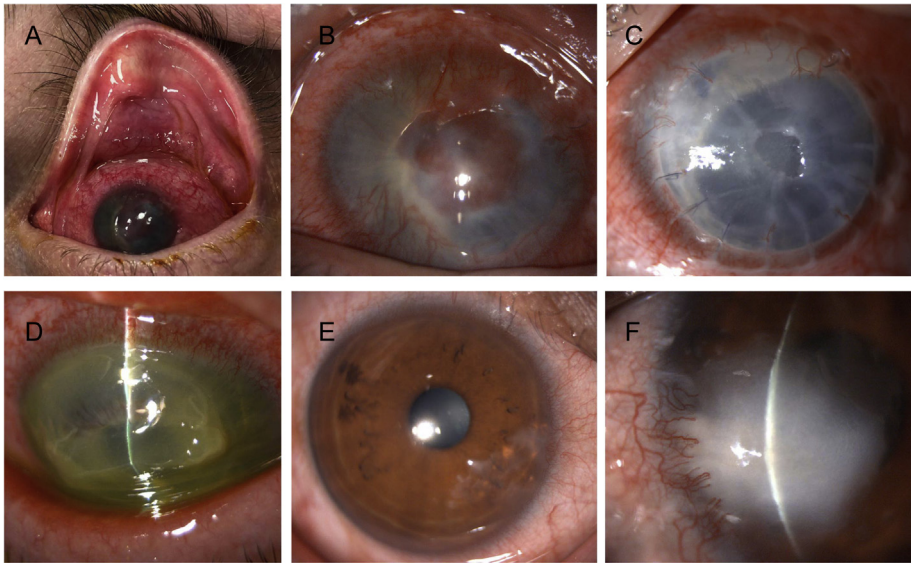

Fig. 1. Case 1 demonstrates extreme laxity of the upper lid, conjunctival hyperaemia, and a perforated central corneal ulcer (A). The cornea was densely vascularised with a large epithelial defect with a central perforation (B). Despite a tarsorrhaphy with lid-shortening, there was continued exposure and at four weeks after penetrating keratoplasty there was continuing ocular surface inflammation with a persistent epithelial defect, loose sutures, and an opaque graft (C). Case 2 showing hyperaemia with a large superior corneal melt that had perforated (D). Case 3 with a nasal hypertrophic scar on the right cornea (E) and dense and vascularised scar on the left cornea (F). This individual usually slept on his left side with his face on the pillow.

Table 2
Corneal signs reported in 104 individuals diagnosed with floppy eyelid syndrome (FES) seen in the 10-year interval from 2008.

Corneal disease	Number (%)
Punctate epithelial keratitis	24 (23.1%)
Corneal vascularisation	4 (3.8%)
Filamentary keratitis	2 (1.9%)
Microbial keratitis	2 (1.9%)
Corneal perforation	2 (1.9%)
Persistent epithelial defect	1 (1.0%)

cases who had severe keratitis, and two of these had corneal ulceration that required a tectonic keratoplasty.

Discussion

FES is most frequently observed in obese males in their third to fifth decade, although it can also affect women and children.[1,3,4] Referral is usually prompted by symptoms of chronic redness, irritation and discharge. There can be an extended interval between the onset of symptoms and the diagnosis of FES.[6] Clinical signs include a combination of easy eversion of the eyelids by skin traction, a lax tarsal plate, and a secondary micropapillary conjunctival reaction.[1,4] Secondary ocular surface disease can be very asymmetric or unilateral,[3,4] which may reflect the preferred side on which patients sleeps, often face down on their pillow or hand. Affected individuals may also have OSA.[4,5] The etiology is likely to be the result of mechanical stress or ischemia of the tarsal plate leading to extracellular remodelling, elastic fibre phenotype alterations and increased collagen turnover.[4,7–10] Management is targeted at prevention of lid eversion and protection of the ocular surface, although extreme lid laxity may mean that multiple procedures are required (cases #1,2).[4]

In the three cases in this series there was a substantial delay between the onset of severe keratitis and identification of FES as the probable causative factor. In each individual there had been a failure to improve, as well as potentially unnecessary investigations and treatments, prior to the diagnosis of FES. Even after the diagnosis of FES was confirmed, the difficulty in surgically preventing lid eversion meant that the ocular surface disease was not easily controlled.

The prevalence of FES is also unknown, as it is an underdiagnosed cause for chronic conjunctivitis or keratitis.[3,4] Not all patients have significant secondary ocular surface inflammation. In a case series of 60 patients (43) 71% had significant signs of corneal disease.[3] The most common corneal change was punctate epithelial keratopathy (45%), but filamentary keratitis, recurrent corneal erosion, microbial infection, vascularization, and scarring and stromal melting also occurred.[3] In that series corneal perforation was secondary to microbial infection or exposure.[3] In contrast, in our retrospective review of 104 individuals only 24 (23%) were recorded to have signs of ocular surface disease. The difference in the prevalence of recorded corneal disease may reflect our preferred primary management pathway of FES in our institution to the oculoplastic service rather than to the corneal service.

In conclusion, severe keratitis can be the presenting feature of FES, but in some individuals the diagnosis of FES can then still be delayed or missed. Therefore, signs of FES should be actively sought in individuals who have chronic conjunctivitis or keratitis, particularly if they are obese. Affected individuals may not volunteer that they have symptoms of a disturbed

sleep pattern until asked directly, and individuals who have associated symptoms of OSA should then be referred for medical review and potential continuous positive airways pressure (CPAP) therapy. This study highlights that the proportion of individuals with FES who have sight loss from corneal complications is low, but that the consequences of a missed diagnosis can be a protracted delay before appropriate treatment is provided, with unnecessary investigation, treatments and clinical deterioration.

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