Clinical characteristics of conjunctivochalasis with or without aqueous tear deficiency

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Aim: To show characteristic ocular surface findings caused by conjunctivochalasis (CCh) in dry eye patients with or without aqueous tear deficiency (ATD).

Design: Comparative non-interventional cases.

Patients and methods: Clinical data of five ATD patients without CCh (group A), eight CCh patients with ATD (group B), and eight CCh patients without ATD (group C) were retrospectively reviewed. Presence or absence of CCh was determined by fluorescein staining to outline tear meniscus and conjunctival folds with an enhancing filter. Dry eye symptoms, history of subconjunctival haemorrhage, meibum expression, tear break up time, fluorescein and rose bengal staining, and fluorescein clearance test, and other abnormal ocular surface findings were measured.

Results: CCh patients were significantly older (p = 0.001). In pure ATD, the principal symptom of dryness became worse as the day progressed. In contrast, blurry vision, burning sensation, and dryness became worse during reading in all CCh patients (p = 0.0008) or worse in the morning upon awakening in the majority patients with CCh only (p = 0.02). Besides the interpalpebral exposure, which was noted in ATD, positive fluorescein or rose bengal staining was noted in the redundant conjunctival folds and the non-exposure zone in CCh (p = 0.0008). Redundant conjunctival folds were present in both lower and upper bulbar conjunctiva, obliterating both lower and upper tear meniscuses, and spatially correlated with anterior migration of the mucocutaneous junction in CCh. Delayed tear clearance was significantly more prevalent in CCh than ATD (p = 0.0008). Vigorous blinking worsened in CCh but not in ATD (p = 0.0008). Lacrimal puncta were swollen in groups B and C, but not in group A (p = 0.04).

Conclusions: CCh is not restricted to the lower bulbar conjunctiva, and contributes to pathogenesis of dry eye by obliterating both lower and upper tear meniscus, causing unstable tear film and by creating delayed tear clearance. Dry eye symptoms were worsened by downgaze during reading and by vigorous blinking. Other characteristic signs including subconjunctival haemorrhage, swollen puncta, anterior migration of the mucocutaneous junction, and patterns of dye staining also help distinguish dry eye associated with CCh from that caused by ATD alone.

C onjunctivochalasis (CCh) defined as “a redundant conjunctiva typically located between the eyeball and the lower eyelid” is not uncommon but often overlooked as a normal ageing variation. CCh tends to be bilateral and can be localised in the nasal, central, or temporal part of the lower eyelid margin. Patients with CCh may be asympomatic, but may manifest dry eye by aggravating a pre-existing unstable tear film caused by aqueous tear deficiency (ATD) at a mild stage, cause episodic tearing by impeding the tear clearance at a moderate stage, and induce subconjunctival haemorrhage and exposure at a severe stage. The association of CCh with keratoconjunctivitis sicca (KCS) was first described by Rieger in 1990 and Grene in 1991, but more thoroughly explored by Höh et al in 1995, who noted the risk of developing KCS increases with severity of CCh. It remains unclear whether KCS caused by ATD alone can be distinguished from KCS caused by CCh, and whether CCh induced dry eye presents unique clinical features even when it is associated with ATD.

Although the exact pathogenic mechanism of developing CCh remains unclear, we postulated that conjunctival looseness might result from excessive degradation of the extracellular matrix. Our hypothesis was supported by our recent study showing that CCh fibroblasts produce more matrix metalloproteinase type 1 (MMP-1) and type 3 (MMP-3) than normal conjunctival fibroblasts in culture. Because such overexpression of MMP-1 and MMP-3 is further upregulated by inflammatory cytokines such as interleukin 1 (IL-1) and tumour necrosis factor α (TNF-α), we speculated that CCh patients should carry signs of ocular surface inflammation. Because we have reported that the tear clearance is delayed in eyes with ocular surface inflammation, and others have reported that delayed tear clearance is associated with elevated tear levels of gelatinase and IL-1 in rosacea patients, we wondered whether delayed tear clearance may help distinguish dry eye with CCh from dry eye without CCh. Liu proposed that inferior loose conjunctiva interferes with tear clearance resulting in epiphora. Nevertheless, it remains unclear whether CCh also disrupts or obliterates the upper tear meniscus. For all these reasons, we have undertaken a retrospective review of clinical data gathered from CCh patients with or without ATD and compared them with those obtained from ATD patients without CCh.

Abbreviations: ATD, aqueous tear deficiency; CCh, conjunctivochalasis; FCT, fluorescein clearance test; KCS, keratoconjunctivitis sicca; LTD, lipoid tear deficiency; MGD, meibomian gland dysfunction; MMP, matrix metalloproteinase; BUT, tear break up time
材料和方法

这项研究获得了位于迈阿密和南迈阿密医院的审评委员会的批准，对过去6个月的临床数据进行了回顾性评估，其中包括5名干眼症患者（A组），8名CCh患者（B组）和8名干眼症患者（C组）。A组的诊断基于Meller和Tseng的报道。CCh的诊断也在Shirmer试验（SFT）中得到了证实。CCh与脂质泪液缺乏症（LTD）的诊断标准是基于荧光素滴眼液在泪液中是否存在。

统计分析

比较了A组和B组患者的历史和 BUT 之间的差异。A组和B组的患者被分为两组进行独立分析。A组和B组的患者在眼部检查中都未发现异常的眨眼。症状在晚上、早晨或阅读时加剧。

结果

相关临床数据见表1和2。

比较A组和B组及C组：CCh相关的差异

A组患者显著年轻于B组和C组（p<0.001）。所有A组的患者中，3组中的异常症状包括干眼症，但在B组和C组中也包括了模糊视野和烧灼感。A组的症状比B组和C组轻，但在进展过程中，A组的症状更为明显。A组的患者在晚上、早晨或阅读时症状更明显。

比较B组和C组：ATD与CCh的差异

在B组和C组中，干眼症的患者与CCh的患者在年龄、BUT和泪液分泌方面存在差异。B组和C组的患者在症状上的差异包括：B组的患者有干眼症、模糊视觉和烧灼感；C组的患者没有干眼症，但也存在模糊视觉和烧灼感。
Ocular surface changes in patients with or without conjunctivochalasis

### Table 2
Ocular surface changes in patients with or without conjunctivochalasis

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<tr>
<th>Case</th>
<th>CCh location</th>
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<th>C</th>
<th>CCh by fast blink</th>
<th>Staining in CCh</th>
<th>Lid margin erosion</th>
<th>Obiterated tears meniscus</th>
<th>Swollen punctum</th>
<th>Pingueculae*</th>
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FCT = fluorescein clearance test measuring the average wetting length (mm) for 1 min with Schirmer strip (with anaesthetic) at 10 and 20 min time points. Reflex = reflex tearing determined by nasal stimulation performed at the 30 min time point (present: wetting length (mm) greater than the above baseline value; absent: wetting length equal to or no greater than the baseline value). DTC = delayed tear clearance measured by FCT (absent: no DTC and is found in normal subjects when dye cleared within 20 min; present: dye clearance was delayed more than 20 min). BUT = tear break up time (seconds). MGD = meibomian gland dysfunction determined by meibum expression (absent: meibum was readily expressed; present: meibum poorly or not expressed by digital compression). PM = as the day progresses; AM = upon awakening; F = female; m = male; FL = fluorescein; RB = rose bengal.

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T = temporal bulbar conjunctiva; N = nasal bulbar conjunctiva; C = central (inferior) bulbar conjunctiva; U/L = upper and lower tear meniscuses. Severity of CCh based on folds of loose conjunctiva: +++, severe; ++, moderate; +, mild; –, absent. Staining in the CCh was determined by rose bengal staining. Lid margin erosion was determined by the presence of anterior migration of the mucocutaneous junction shown by fluorescein staining in or near CCh. Obliterated tear meniscus was determined by fluorescein staining. +, positive or present; –, negative or absent. Severity of floppy eyelids was graded as 1+ when less than 1/3 of the upper tarsus was visible after lid eversion, 2+ when up to 1/3 of the upper tarsus was visible, and 3+ when more than 1/3 of the upper tarsus was everted. *Pingueculae were present in both nasal and temporal bulbar conjunctiva.
DISCUSSION

CCh patients were significantly older than ATD patients without CCh, consistent with the notion that CCh is associated with ageing.9 11–13 Dryness was worse as the day progressed in ATD due to progressive exposure and desiccation throughout the day. In contrast, CCh patients also complained of additional blurry vision and pain, both of which tended to be worse when reading. This is because CCh folds are increased by downgaze during reading. On the contrary, the interpalpebral exposure zone increases from downgaze to upgaze,14 explaining why ATD dry eye is worse in upgaze, especially when working with a computer screen.15 Therefore, differences in symptoms upon upgaze (computer work) or downgaze (reading) help differentiate pure ATD induced dry eye from CCh induced dry eye. Furthermore, frequent blinking exacerbated CCh, resulting in the spread of conjunctival folds to the 6 o’clock position, further aggravating blurring vision and dryness. In contrast, increasing blinking shortens the inter-blink interval, invariably stabilising the tear film and improving ATD dry eye.16 Furthermore, if ATD patients also had CCh, symptoms were worse in the morning upon awakening because delayed tear clearance is worsened during sleep (also see below).

Traditionally, CCh is recognised only in the lower aspect.1 The present study, however, revealed that CCh was also found in the upper aspect. This was best demonstrated by fluorescein staining to delineate the tear meniscus, especially with the aid of a special filter. Interruption or obliteration of the tear meniscus by temporal CCh becomes apparent when fluorescein is used, and is noted in both the lower and upper lids (C and D) and by nasal CCh (D) (stars and arrow respectively). (E and F) In this representative patient with severe CCh without ATD, obliteration of the tear meniscus by temporal CCh becomes apparent when fluorescein is used, and is noted in both the lower and upper lids (C and D) and by nasal CCh (D) (stars and arrow respectively). (G and H) Another representative patient with more severe CCh without ATD, obliteration of the tear meniscus by temporal CCh becomes apparent when fluorescein is used, and is noted in both the lower and upper lids (C and D) and by nasal CCh (D) (stars and arrow respectively). Inset shows the corresponding control without fluorescein.

Figure 1  Fluorescein staining showing obliteration of tear meniscus of lower and upper lids by CCh. (A) In this representative ATD patient without CCh, there is continuous low tear meniscus of the lower and upper lids. (B to D) In this representative ATD with severe CCh, conjunctival folds were noted in the temporal bulbar conjunctiva (B). However, even if the meniscus was low, obliteration of the tear meniscus by temporal CCh becomes apparent when fluorescein is used, and is noted in both the lower and upper lids (C) and by nasal CCh (D) (stars and arrow respectively). (E and F) In this representative patient with severe CCh without ATD, obliteration of the tear meniscus of the lower lid (stars) and of the upper lid (arrows) by conjunctival folds is noted in both temporal and nasal bulbar conjunctiva, respectively. (G and H) Another representative patient with more severe CCh without ATD, obliteration of the tear meniscus by temporal CCh becomes apparent when fluorescein is used, and is noted in both the lower and upper lids (C and D) and by nasal CCh (D) (stars and arrow respectively). (E and F) In this representative patient with severe CCh without ATD, obliteration of the tear meniscus by temporal CCh becomes apparent when fluorescein is used, and is noted in both the lower and upper lids (C and D) and by nasal CCh (D) (stars and arrow respectively). Inset shows the corresponding control without fluorescein.

Figure 2  Worsening of CCh after vigorous blinking and anterior migration of the mucocutaneous junction and CCh shown by fluorescein staining. (A and B) Conjunctival folds noted in the 6 o’clock position (A) become much worse by covering more inferior cornea (B, arrow) after vigorous blinking. (C and D) In a representative CCh patient without ATD, signs of inflammation of the temporal lid margin are observed in the lower lid, especially under higher magnification. (E and F) In the same patient as C and D, obliteration of tear meniscus and conjunctival folds are noted in the lower (stars) and upper (arrow) lids of the right eye (E) and the left eye (F). The extent of CCh is worse in the left eye than the right eye and tear meniscus was pooled before conjunctival folds in the left eye. (G and H) In the same patient, when an enhancing filter is used, obliteration of tear meniscus (see arrow in G) and conjunctival folds become more obvious (compare with E). In addition, erosion leading to anterior migration of the mucocutaneous junction becomes more apparent (stars) immediately adjacent to CCh. Under higher magnification, such migration is noted passing orifices of meibomian glands.
In pure ATD, an unstable tear film tends to develop at the interpaperal exposure zone, which is characteristically stained by rose Bengal. By interrupting or obliterating tear menisci, CCh destabilises the tear film immediately above the CCh area. That was why dye staining decorated the area above the redundant conjunctival fold in a linear pattern (fig 3C and D). That was also why rose Bengal stained CCh areas, which upon pulling down the lower lid spread to the non-exposure zone (inferior to the exposure zone) as previously reported, and the adjacent mucosal surface of the lid margin (fig 3D). If CCh progressed to the 6 o’clock position, the tear film would break up at the inferior corneal/limbal area, a pattern different from random tear break up of the cornea in pure ATD.

Another striking finding of CCh was its spatial correlation with anterior migration of the mucocutaneous junction. This pathology is presumably caused by overspill of aqueous tears due to the space occupying effect and obliteration of the tear meniscus by CCh (fig 2F). As a result, regional lid margin meniscus, CCh destabilises the tear film immediately above the redundant conjunctival fold in a linear pattern (fig 3A). As patients in group A were young, and all older patients with ATD would have some extent of CCh and MGD, it is important to determine if CCh contributes to the development of dry eye irritation by tear film instability (dry eye), delayed tear clearance, or inflammation. Clinical characteristics of CCh described herein help us look into such pathogenic mechanisms as interruption or obliteration of tear meniscus, ocular surface inflammation, delayed tear clearance, and anterior migration of the mucocutaneous junctions. Accordingly, we also believe treatments should include anti-inflammatory therapies. When medical treatments fail, the ultimate solution might be to resort to surgical correction of tear spread and clearance caused by CCh. Recognition of CCh in dry eye patients is thus of utmost important to devise effective treatment plans.

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REFERENCES

Figure 3 Swollen puncta and rose bengal staining. (A) Normal appearance of lower and upper puncta in an ATD patient. (B) Swollen puncta with elongation and subcutaneous oedema of lower and upper puncta in a CCh patient. (C and D) Under normal light and a green filter, respectively, rose bengal staining is detected at non-exposure zone (inferior limbal region), pingocele (exposure zone), and the mucosal surface of the inferior lid margin (due to CCh in the region) in a CCh patient without ATD.