REVIEW ARTICLE

Conjunctivochalasis: A Review Article

Conjuntivocalásia: Um Artigo de Revisão

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ABSTRACT

Conjunctivochalasis is a chronic conjunctival condition often underdiagnosed. The hallmark is loose, redundant conjunctival folds classically located in the inferior conjunctiva. It is often bilateral and the prevalence rates increase dramatically in the elderly. The exact pathogenesis remains unknown. Conjunctivochalasis has been strongly correlated with aging and concomitant dry eye disease. The currently recognised pathophysiology is associated with mechanical friction, tear film instability, delayed tear clearance, and ocular surface inflammation. Not all cases of conjunctivochalasis are symptomatic or clinically significant. Depending on the severity, it can lead to a spectrum of symptoms, ranging from exacerbation of a dry eye disease in mild forms, to the interference with physiological tear outflow in moderate forms, or even to exposure complications in rare severe cases. The diagnosis of conjunctivochalasis is clinical and mainly supported on a thorough history of symptoms and biomicroscopic findings. No specific treatment is required for the asymptomatic cases. When the disease is symptomatic, the therapeutic approach starts with the medical treatment. For refractory cases, an arsenal of surgical interventions is currently available as a second-line approach.

KEYWORDS: Conjunctival Diseases/diagnosis; Conjunctival Diseases/epidemiology; Conjunctival Diseases/pathology; Conjunctival Diseases/therapy; Dry Eye Syndromes; Ophthalmologic Surgical Procedures.

RESUMO

A conjuntivocalásia é uma doença crónica da conjuntiva frequentemente subdiagnosticada. Tem como principal característica a presença de pregas de conjuntiva laxa e redundante, classicamente localizadas na conjuntiva inferior. É frequentemente bilateral e a sua prevalência aumenta dramaticamente nos idosos. O exato mecanismo patogénico permanece ainda desconhecido. A conjuntivocalásia tem sido fortemente relacionada com o envelhecimento e a presença concomitante de doença de olho seco. A patofisiologia atualmente reconhecida está associada com fricção mecânica, instabilidade do filme lacrimal, atraso de drenagem lacrimal e inflamação da superfície ocular. Nem

todos os casos de conjuntivocalásia são sintomáticos e clinicamente significativos. Dependendo da gravidade, pode levar a um vasto espectro de sintomas que inclui desde a exacerbação da doença do olho seco em formas ligeiras, à interferência no fluxo lacrimal fisiológico nas formas moderadas ou, raramente, a complicações por exposição nos casos severos. O diagnóstico é clínico e principalmente suportado por uma história clínica detalhada e achados biomicroscópicos. Nos casos assintomáticos não é necessário qualquer tratamento específico. Na presença de doença sintomática, a abordagem terapêutica inicia-se com o tratamento médico. Nos casos refratários, várias intervenções cirúrgicas estão atualmente disponíveis como abordagem de segunda linha

PALAVRAS-CHAVE: Doenças da Conjuntiva/diagnóstico; Doenças da Conjuntiva/epidemiologia; Doenças da Conjuntiva/patologia; Doenças da Conjuntiva/tratamento; Procedimentos Cirúrgicos Oftalmológicos; Síndromes do Olho Seco.

INTRODUCTION

Conjunctivochalasis (CCH) is a common, chronic conjunctival condition often underdiagnosed on clinical practice. The hallmark of CCH is loose, redundant, non-edematous conjunctival folds, typically located in the inferior bulbar conjunctiva overlying the lower eyelid margin.[1-3]

CCH can lead to a spectrum of symptoms, ranging from exacerbation of a dry eye disease (DED) in mild forms, to the interference with physiological tear outflow in moderate forms, or even to exposure complications in severe cases. Clinical diagnosis mainly based on biomicroscopic findings helps to distinguish CCH from other common ocular surface disorders that may cause similar complaints. It is typically a bilateral disorder and the prevalence rates increase dramatically in the elderly, as it may be considered a normal senile change.[1] Although it is a frequent cause of ocular surface inflammation, the exact pathogenesis of the disease is not yet fully understood.[4-7]

This review aims to compile the pivotal clinical knowledge about the pathogenesis, clinical features and treatment modalities of CCH.

METHODS

To compile this review, a primary literature search was conducted using the MEDLINE database. The keywords "conjunctivochalasis" and "redundant conjunctival folds" were used in the PubMed search. A secondary literature search was conducted by reviewing the references of the initially included articles. Articles up to the year of 1998 were included.

EPIDEMIOLOGY

CCH is a common ocular disorder, frequently seen in the elderly.[7] However, it may be diagnosed in a wide range of ages, even in young subjects. It is often a bilateral condition but it can be asymmetrical or unilateral.

The precise prevalence in contemporary European and American populations is unknown. CCH is thought to be more frequent in Asiatic populations. In a Chinese community-based study, the prevalence of total and clinically significant CCH among people 60 years or older was 44% and 18%, respectively.[8] A Japanese hospital-based study demonstrated a surprising prevalence rate of 98% or more in individuals older than 60 years.[9] In contrast, a study from Iran showed a prevalence of only 6.2% among participants aged 45 to 69 years.[10]

RISK FACTORS AND ASSOCIATED FEATURES

Although the exact pathological mechanism underlying CCH remains unclear, many factors have been associated with the development of redundant conjunctival folds.

The increasing age has been strongly correlated with the development of CCH.[10,11] The prevalence rises dramatically with age and it is most commonly diagnosed in the elderly. Mimura *et al* reported in a Japanese study a strikingly higher prevalence with increasing age; prevalence rates for each decade of life from the first to the tenth decades were 7%, 36%, 62%, 71%, 90%, 94%, 98%, 99%, 99%, and 100%, respectively.[9] Zhang *et al* reported a similar effect in a Chinese study; prevalence rates were 37% in 60-70 years, 44% in 71-80 years, 43% in 81-90 years, and 50% in 91-100 years.[8] Additionally, the severity of the disorder, based on the number and height of folds, also have been shown to increase with aging.[12,13] This was confirmed using anterior segment optical coherence tomography (AS-OCT) that also showed a significant age-dependent increase in CCH severity.[7]

The prevalence and severity of CCH was found to be higher in women.[9] A Japanese study reported a total prevalence rate of 85% in females and 75% in males.[13]

There is a strong association between CCH and DED.[1,14] CCH can lead to an unstable tear film and cause dry eye symptoms. Particularly, nasal CCH was associated with a higher risk of DED when compared with non-nasal CCH patients.[5,15] In its turn, the vicious cycle of ocular surface inflammation present in DED can be a predisposing factor to CCH.

Mimura *et al* showed in 600 contact lens wearers compared with an age matched non-wearers population that

the use of contact lenses induces a higher risk of CCH and higher severity grade. Particularly, ocular surface symptoms were significantly higher in hard contact lens wearers.[16]

CCH was found more frequently in hyperopic eyes with higher severity grade.[17] In addition, short axial length eyes (≤20 mm) showed higher grades of temporal and nasal CCH compared with medium (22-24 mm) and long (>24 mm) axial length eyes. The role of axial length on CCH has been speculated to be attributed to the lower surface conjunctival tension and the effects of malposition of the lower eyelid on the conjunctiva, leading to conjunctival redundancy.[18]

Francis *et al* have suggested the potential role of ultraviolet radiation on the development of CCH in a study that found elastotic degeneration in conjunctival specimens of affected subjects.[19] The cumulative exposure to ultraviolet radiation might also contribute to the age-dependent increase in CCH prevalence. It has also been stated an association between the development and severity of pinguecula and CCH, speculating that the effect of aging and ultraviolet radiation exposure can play a role in both ocular disorders.[10,13]

A higher prevalence of CCH was also found in patients with autoimmune thyroid diseases, Ehlers-Danlos syndrome, autosomal recessive cutis laxa and the use of the angiotensin II receptor antagonist losartan.[2]

PATHOGENESIS

The precise mechanism is still a matter of debate. Given the effect of age in the disease prevalence and severity, CCH has been considered a physiological senile change.[1,4] It has been proposed that an age-related reduction in subconjunctival connective tissue leads to the misattachment of the bulbar conjunctiva to the underlying sclera and to conjunctival laxity. This can lead to chronic mechanical friction during blinking and eye movements and triggers a vicious inflammatory cycle that further plays a perpetual role in CCH pathogenesis by degrading extracellular matrix.[20,21] Currently, the recognised risk factors for CCH are associated with mechanical friction, tear film instability, delayed tear clearance, or ocular surface inflammation.

Biochemical studies have found an overexpression of pro-inflammatory cytokines - tumor necrosis factor-α and interleukin-1β - with consequent overexpression of matrix metalloproteinases - MMP-1, MMP-3, and MMP-9 – in conjunctival specimens of CCH.[22,23] This up-regulation of matrix metalloproteinase activity may facilitate the degradation of elastin and collagen fibers in subconjunctival connective tissue, resulting in a redundant conjunctiva.

The role of ocular surface inflammation in the pathogenesis of CCH is further elucidated by the significantly higher levels of proinflammatory cytokines found in tears of affected patients.[24,25] The chronic mechanical friction combined with the loss of lubrication due to DED also promote the generation of pro-inflammatory cytokines.[22,23]

The redundant conjunctival folds can cause an anatomical blockage of the lacrimal punctum and obliteration of the tear meniscus leading to a substantial obstruction of the tear flow. The delayed tear clearance can increase the levels of pro-inflammatory cytokines, matrix metalloproteinases, and oxidative stress-related proteins in tears of CCH patients causing pooling on the ocular surface and amplifying the inflammatory cycle.[26–29] In addition, CCH can also cause tear film instability given that the conjunctival folds interfere with the tear flow from the tear reservoir in the fornix to the tear meniscus, mimicking a state of aqueous-deficient DED.[26,28] Furthermore, the inadequate spreading of lipids over the ocular surface may additionally contribute to tear film instability by causing lipid-deficient DED.[30,31]

HISTOPATHOLOGY

Few evidences have been published concerning histopathological changes on CCH. Some studies have found conjunctival epithelium hyperplasia.[32] Ward *et al* noted a decreased epithelial cohesiveness.[21] Some studies have reported that abnormalities of elastic fibers, such as fragmentation, accumulation, or reduced number, may play an important role in the disease pathogenesis by causing conjunctival relaxation.[11,33] Lymphangiectasia was found to be more frequent.[34] Zhang *et al* reported an infiltration of lymphocytes and plasmocytes, and Francis *et al* noted a chronic non-granulomatous conjunctivitis in conjunctival samples.[32,35] However, there is a lack of strong evidence about the histopathological changes and it is not clear whether such findings are due to CCH itself. Instead, loose attachment of the conjunctiva to the underlying sclera may be the major pathological mechanism in CCH.

CLINICAL FEATURES

Depending on the severity of the condition, not all cases of CCH are clinically significant. It is often an asymptomatic ocular surface disorder. When symptomatic, it can cause a wide range of symptoms attributable to tear film instability or delayed clearance, ocular surface inflammation, and mechanical compression of the redundant conjunctiva during blinking and eye movements.[2]

Ocular dryness, irritation, discomfort, transient blurred vision, asthenopia, pain, burning, foreign body sensation, and episodic tearing can be found if DED is the prominent feature.[1,5,36] However, symptoms of tear overflow like epiphora and mucus discharge can also be described in cases of significant blockage of tear flow, delayed tear clearance and punctal occlusion.[37,38] One study showed that nasal CCH causes more dry eye symptoms, ocular pain and punctal displacement or occlusion than non-nasal CCH.[5]

Conjunctival hyperemia with injected vessels and superficial punctate keratitis is often observed.[13,29] Subconjunctival hemorrhage, usually inferior, is frequent and occurs due to the rupture of subconjunctival vessels of the redundant inflamed conjunctiva.[12] Sudden, sharp, and intermittent pain intensified by downgaze is thought to be derived from the compression of the redundant conjunctiva during eyelid blinking or closure.[1] Blepharitis which is caused by retention of debris or excess of aqueous tears may also be observed.

In cases of severe CCH, the folds may overlap the inferior limbus and cornea; there may be present some degrees of lagophthalmos and even marginal corneal ulcer can occur with dellen formation.[2]

SEVERITY GRADING

Several severity scores based on slit lamp biomicroscopic findings have been proposed to classify CCH.

Meller and Tseng have proposed a comprehensive grading system based on multiple parameters (Table 1).[1] This system defines the extension and location of the redundant conjunctiva regarding to the lower eyelid. For each location, the height of folds is further characterized regarding to the tear meniscus height. For nasal CCH, the extent is subdivided as to whether it occludes the inferior punctum or not. Additionally, the effect of downgaze and digital pressure on the height and extent of CCH is described.

DIAGNOSTIC APPROACH

The diagnosis of CCH is clinical and mainly supported on a thorough history of symptoms and biomicroscopic findings. It can be a challenging diagnosis given the low specificity of CCH symptoms and the great overlap with other common ocular surface disorders, such as DED, Meibomian gland dysfunction, floppy eyelids and anterior or posterior blepharitis.

CCH should be suspected in all subjects that present with ocular surface irritation and symptoms of DED or lacrimal obstruction, particularly in the elderly and if non-responders to the conventional treatments.[2] Worsening of symptoms in downgaze during reading or computer usage or by vigorous blinking may point to the diagnosis of CCH, instead of worsening in upgaze that is a typical feature of DED due to the increased ocular surface exposure.[26] It should also be considered in patients with recurrent subconjunctival hemorrhage.[39]

Slit lamp examination of the anterior segment clearly reveals the redundant conjunctival tissue arranged in parallel folds over the inferior eyelid margin which move with blinking. Folds are often bilateral and can be located in the temporal, sub-limbal, and nasal regions of the lower eyelid; in severe cases they spread along the whole lower eyelid. The folds typically increase by pressing the lower eyelid against the globe upwardly, and they disappear on upgaze and by pressing the lower eyelid away from the globe. Superior CCH may be less obvious to identify; they can be demonstrated more clearly by pressing the upper eyelid against the globe downwardly. Additional findings may include conjunctival hyperemia with injected vessels on the redundant bulbar conjunctiva, as well as swollen lacrimal puncta.[1,2]

Ocular surface staining with fluorescein, rose Bengal, or lissamine green can help to elucidate the redundant conjunctival folds and demonstrates the status of the precorneal tear film and tear meniscus or the presence of corneal punctate erosions.

The reduced tear film stability can be demonstrated using the fluorescein tear film break-up time.[30] Furthermore, tear clearance rate can be assessed using the fluorescein clearance test, which may show a delayed clearance.[27,40] Increased tear film osmolarity may be found in severe cases, especially if abnormal break-up time and positive ocular surface staining are present.[41]

AS-OCT has been recently used to facilitate the precise grading of CCH. Cross-sectional scans of the conjunctiva allowed to precisely measure the area of the conjunctival folds. It also permits quantification of the tear film parameters, such as the area, height and volume of the tear meniscus.[42,43] Furthermore, ocular surface inflammation can be quantitatively determined by measuring tear film inflammatory markers and conjunctival inflammatory cell infiltrates.[20]

Intraoperatively, CCH can be easily confirmed by ''tenting'' the loose conjunctival tissue using forceps.

THERAPEUTIC APPROACH

No specific treatment is required for the asymptomatic cases – the vast majority of patients. When the disease is

Table 1. Grading System for Conjunctivochalasis[a]

Location	Folds Height	Punctal Occlusion	Changes in Downgaze	Changes by Digital Pressure
0 1 2 3	A B C	O + O -	G Ý G Û G ß	P Ý P Û P ß
0: none 1: one location 2: two locations 3: whole lid	A: < tear meniscus B: = tear meniscus C: > tear meniscus	O +: nasal location with punctal occlusion O -: nasal location without punctal occlusion	G Ý: height/extent of chalasis increases in downgaze G Û: no difference G ß: height/extent of chalasis decreases in downgaze	P Ý: height/extent of chalasis increases on digital pressure P Û: no difference P ß: height/extent of chalasis decreases on digital pressure

[a] The grading system defines the extension of redundant conjunctiva as grade 1 = one location, 2 = 2 locations, 3 = whole lid. For 1 and 2, it is further specified as T, M, and N if conjunctivochalasis is found in the temporal, the middle, and the nasal aspect of the lower lid, respectively. For each location, further notation is given to indicate if the height of folds is less than (A), equal to (B), or greater than (C) the tear meniscus height. If it is found in the nasal (N) location, the extent of chalasis is further determined as to whether it occludes the inferior puncta. For each location, it is further graded as G Ý if its height is greater than, as G Û if equal to, and as G ß if less in downgaze (G) than the previous height of the folds. Likewise, it is further graded as P Ý, P Û and P ß if it is worse, no difference, or better with digital pressure (P), respectively.

symptomatic, the first therapeutic approach is the medical treatment. Given the high rates of clinical overlap, coexistent ocular surface conditions should be ruled-out and addressed concurrently in order to achieve maximal symptom relief. Only for the non-responders to conservative measures, an arsenal of surgical interventions is currently available as a second-line approach.

Medical Treatment

Medical therapy for CCH aims to target tear film dysfunction and ocular surface inflammation – two major pathogenic mechanisms that lead to conjunctival weakness.

Topical lubrication improves tear function and stability and reduces the mechanical friction between redundant bulbar conjunctiva and the eyelids.[44] It can be performed using eyedrops or ointments. Enhanced lubrication was proven to effectively decrease the severity grade of CCH in a study reporting the use of a 3-month course of artificial tears containing isotonic glycerol and 0.015% sodium hyaluronate 4 times a day.[45] In more severe cases, autologous serum eye drops may also be used to further achieve a more functional tear status.[6]

Topical corticosteroids were employed to target the vicious cycle of inflammation in CCH. Prabhasawat *et al* showed that the use of topical non-preserved 1% methylprednisolone 3 times a day for 3 weeks leads to subjective (83%) and objective (80%) improvement in the severity grade of CCH and improved tear clearance.[29,36]

In rare instances of severe CCH causing nocturnal lagophthalmos, eye patching should be considered as a temporary measure to prevent conjunctival desiccation. Bandage contact lenses can also be used temporarily to displace the conjunctival folds.[3]

Surgical Treatment

A variety of surgical procedures may be undertaken to address refractory CCH. Surgical treatment is directed at excising or attaching the redundant conjunctiva. The major goal is to eliminate its influence with the tear meniscus and smoothen the conjunctival surface to reduce the mechanical trauma. Among all surgical procedures reported, conjunctival cauterization and simple excision are the most popular.

Conjunctival Cauterization

Conjunctival cauterization may be considered as a first surgical option to address refractory cases of mild to moderate CCH. It leads to coagulation and shrinkage of the loose redundant conjunctiva with conjunctival attachment to the underlying Tenon's capsule and episcleral tissue.[46,47]

Different techniques have been described for conjunctival cauterization under topical or subconjunctival anesthesia. Cautery is applied with coagulation forceps over the redundant conjunctiva, typically 5 mm posterior to the limbus.[3] In general, a complete or major improvement in CCH symptoms have been reported in 84%–100% of patients after this procedure.[3,48,49]

Compared with excisional techniques, it was shown as effective but with earlier symptom relief. However, repeated procedures may be required to achieve surgical success.[46,47,50] Recurrence rates can be high if an incomplete initial treatment is performed.[3]

Cauterization spares the possible suture-related complications, excessive scarring and prevents removal of normal conjunctival tissue or motility restriction. It is a relatively simple procedure that allows short surgical and recovery times. Self-limited postoperative adverse events such as foreign body sensation, mild irritation, mild pain, conjunctival hyperemia, chemosis, and subconjunctival hemorrhage have been reported after cauterization.[2,3]

Conjunctival Excision with or without Tissue Graft

Surgical excision of the redundant conjunctiva, either locally or along the entire inferior bulbar surface, may be considered in patients with mild to severe CCH. Several surgical methods have been proposed over the last decades.

Simple conjunctival excision with direct closure has been in use for many years to treat CCH, leading to complete or substantial improvement in ocular surface symptoms.[40,51] In this procedure, the specific area of loose, redundant conjunctiva is excised and the remaining conjunctiva is sutured. Crescent-shaped, elliptical, or even limbal peritomy-based excisions were employed over the last decades. The success rates range from 84.8% to 93.3%.[3] The major concern regarding the success of this technique is the difficulty to determine the exact amount of the conjunctiva to be excised.[38,52,53] Underresection may be non-therapeutic with persistent symptoms. Overresection or excessive scarring may compromise the inferior conjunctival fornix and lead to cicatricial entropion of the lower eyelid or limit ocular movements. Furthermore, suture placement extends the surgical time, delays healing and is not free of suture-related complications. Postoperative discomfort and foreign body sensation, pyogenic granuloma, giant papillary conjunctivitis, and induction of inflammation may occur.[38]

Conjunctival excision with fibrin glue-assisted conjunctival closure aims to avoid suture-related complications, increases patients' postoperative comfort, and decreases the operating time.[54] Fibrin glue is used to attach the remnant conjunctiva to the underlying scleral tissue. The improvement of symptoms occurs in 89% and all eyes develop a smooth and stable conjunctival surface.[3] More recently, Doss *et al*. proposed the "Paste-Pinch-Cut" conjunctivoplasty procedure. Fibrin glue is injected in subconjunctival space, allowed to polymerize during 20 seconds, while the redundant conjunctiva is grasped with forceps and resected at the final step.[55]

Simple conjunctival excision with primary healing wound closure was evaluated in a study by Petris *et al*. After excising the redundant conjunctiva, the bare sclera was allowed to heal by itself. A significant clinical improvement was found postoperatively, however, a high recurrence rate of 24% was reported.[56]

Conjunctival excision with tissue graft has been recently introduced and showed a significant clinical improvement.[37,57] The use of amniotic membrane transplantation to cover the bare sclera avoids excessive scarring and enhances the proliferation of epithelial and goblet cells to effectively reconstruct the physiological conjunctival surface. For amniotic membrane placement sutures may be employed, but the use of fibrin glue showed higher postoperative comfort, decreased surgical time, and avoids suture-related complications.[31,58]

A modification of amniotic membrane technique has been recently reported with promising results to manage superior CCH. The technique called "Tenon reinforcement" implies the removal of excessive Tenon tissue without conjunctival excision, placement of the amniotic membrane over the bare sclera assisted by fibrin glue and suture of the conjunctival flap on the top of the amniotic membrane.[59]

Conjunctival Scleral Fixation

Scleral fixation of the redundant conjunctiva is an alternative technique to treat inferior CCH. In this procedure, the loose conjunctival tissue is firmly attached to the underlying sclera with vicryl sutures 8 mm posterior to the inferior limbus. This technique avoids conjunctival resection, inferior fornix shortening or ocular motility restriction.[60]

Other Alternatives

Other minor techniques were reported to address CCH. Conjunctival ligation implies the aspiration of the conjunctival folds using a tube, followed by tightening and excising of the redundant tissue. Laser conjunctivoplasty using argon or near-infrared laser induces coagulation and shrinkage of the redundant conjunctiva with minimal adverse effects.

CONCLUSION

CCH is a chronic ocular surface disease characterized by the formation of loose, redundant folds mostly located in the inferior bulbar conjunctiva. Despite the high prevalence among older patients, this condition is frequently overlooked in clinical practice. The development of CCH has been strongly correlated with increasing age and concomitant DED. The exact pathophysiological mechanism is still unclear. However, chronic mechanical friction and chronic ocular surface inflammation seems to play a perpetual role in the disease pathogenesis by triggering the extracellular matrix degradation. CCH is often a silent, asymptomatic disorder. When symptomatic, it can lead to significant ocular morbidity by increasing symptoms of DED, exacerbating tear overflow symptoms of a pre-existing lacrimal obstruction or merely by causing ocular surface irritation, pain, and foreign body sensation. The diagnosis of CCH is clinical and mainly based on symptoms and biomicroscopic findings. An asymptomatic disease needs no treatment and can only be observed over time. For symptomatic subjects, enhanced lubrication and topical steroids are the first line therapy for symptom relief. Surgical procedures may be undertaken in refractory cases and most often comprise simple techniques of cauterization or excision of the redundant tissue. Currently, the early diagnosis and relatively high success rates described with the surgical approaches prevented the exposure complications of severe cases reported in the past.

The main goal of this review is to raise awareness for the importance of this condition in daily clinical practice given its high prevalence and associated morbidity. A high suspicion index should be maintained when evaluating subjects that present with ocular surface complaints and symptoms of dry eye or lacrimal obstruction, considering that medical treatment and technically easy surgical approaches for CCH showed high rates of success.

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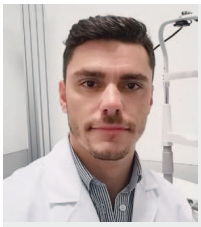

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