Review

Adenoviral keratoconjuntivitis: An update

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ABSTRACT

The objective of this review is to describe the clinical and epidemiological characteristics of adenoviral conjunctivitis, as well as to present a practical update on its diagnosis, treatment and prophylaxis.

There are two well-defined adenoviral keratoconjunctivitis clinical syndromes: epidemic keratoconjunctivitis and pharyngoconjunctival fever, which are caused by different adenovirus serotypes. The exact incidence of adenoviral conjunctivitis is unknown. However, cases are more frequent during warmer months. Contagion is possible through direct contact or fomites and the virus is extremely resistant to different physical and chemical agents. The symptomatology of conjunctival infection is similar to any other conjunctivitis, with a higher incidence of pseudomembranes. In the cornea, adenoviral infection may lead to keratitis nummularis. Diagnosis is mainly clinical, but its etiology can be confirmed using cell cultures, polymerase chain reaction or immunochromatography. Multiple treatments have been tried for this disease, but none of them seems to be completely effective. Prevention is the most reliable way to control this contagious infection.

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Queratoconjuntivitis adenovíricas: actualización

RESUMEN

El objetivo de esta revisión es resumir las características clínicas y epidemiológicas de las queratoconjuntivitis adenovíricas (QCA), así como presentar una actualización práctica sobre el diagnóstico, tratamiento y prevención de estas infecciones oculares.

Dentro de las QCA, existen dos síndromes clínicos claramente diferenciados, la queratoconjuntivitis epidémica y la fiebre faringoconjuntival, que están causados por diferentes serotipos de adenovirus. Su incidencia exacta es desconocida, y los casos son más frecuentes durante los meses cálidos. El contagio se produce mediante contacto directo y por fomites, y los virus son extremadamente resistentes a diferentes agentes físicos y químicos. La sintomatología conjuntival es semejante a la de otras conjuntivitis, con una mayor predilección por la formación de pseudomembranas. En la córnea, la infección adenovírica puede producir infiltrados subepiteliales. El diagnóstico es fundamentalmente clínico, aunque el

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Introduction

Infectious keratoconjunctivitis due to adenovirus is an extremely frequent ophthalmological disease produced by various serological subtypes of human adenovirus (HAV) which can present with various symptoms and signs. As there is no exact correlation between the HAV serotypes and the clinical expressions they produce, adenoviral keratoconjunctivitis (AKC) is the term used to define ocular surface infections produced by any of the known HAV serotypes.

AKC comprises 2 clearly differentiated clinical syndromes, i.e., epidemic keratoconjunctivitis (EKC) and pharyngoconjunctival fever (PCF).

The objective of this review is to summarize the clinical and epidemiological characteristics of AKC and to present a practical update on the diagnosis, treatment and prevention of said ocular infections.

Microbiology

Adenovirus were first described in 1953 by Rowe et al. who observed that the human lymphoid tissue suffered a characteristic spontaneous degeneration when maintained in culture several weeks after surgical extraction. In 1955, Jawetz et al. were the first to attribute the etiology of EKC to the infection of ocular surface tissue caused by HAV.

Since their discovery, 51 different types of adenovirus have been described. Among them, 7 have high affinity with the conjunctival epithelium and can produce AKC (serotypes 3, 4, 5, 7, 8, 11, 19, 37). Adenovirus are virus with double-stranded DNA having 90–100 nm diameter, without cover and with icosahedral capsid having 20 sides and 12 vertices, made up of 252 subunits called capsomeres. DNA has a molecular weight of $23 \times 10^6$ Da, and represents 10–15% of the virus mass.

HAV are very stable against chemical and physical agents as well as in adverse pH conditions. This allows them to survive for long periods of time outside the body and water. Studies have demonstrated that they are able to remain feasible maintaining infectious concentrations even after 28 days on a metal or plastic surface.

Epidemiology

AKC is one of the most frequent ocular diseases, exhibiting ubiquitous distribution. Due to its high frequency and that many of the cases do not obtain medical help it is impossible to develop precise statistics about its incidence. In addition, there are no reliable data about the social and health costs caused by this disease.

HAV can give rise to epidemic outbreaks both in the general population and in hospital environments. In fact, AKC is the most frequent hospital ophthalmological disease. The incidence of AKC, particularly the one related to serotypes 3, 4 and 37, increases in summer when temperature rises. EKC outbreaks have been mainly associated to serotypes 8, 19 and 37, while PCF cases have been related more with serotypes 3, 7 and 11.

The most frequent transmission of HAV is direct from person to person through the respiratory or fecal-oral pathways, although transmission can also appear through fomites. The virus can be easily isolated from ocular secretions of patients for at least 9 days since the onset of symptoms. In the ophthalmology practice there is a risk of transmission through contact tonometry, use of eyedrops and through the hands of health professionals. In the general population the risk of contagion from the patients to domestic contacts is of approximately 10%, with the risk increasing in cases of prolonged disease.

Clinical syndromes

HAV infections can produce 2 different clinical syndromes with ocular involvement: EKC and PCF.

Epidemic keratoconjunctivitis

EKC is a form of conjunctivitis that produces epidemic outbreaks in hospitals, swimming pools, barracks, schools and other communities. The incubation period varies between 4 and 24 days and, even though it is likely that the disease is no longer contagious during this period, Kimura et al. did not find virus through the polymerase chain reaction (PCR) in conjunctival exudates obtained previously at the onset of symptoms. EKC is a slow onset and predominantly
The underlying conjunctiva without damaging the epithelium by means of peeling, producing minor bleeding, if any.

The appearance of subepithelial infiltrates (Fig. 3) is an additional frequent EKC complication which can be observed in up to 50% of cases. Said infiltrates are particularly frequent in serotype 8 infections. In addition, they are considered to be pathognomonic of adenoviral infection and generally appear when the conjunctivitis begins to resolve. It is believed that these infiltrates are due to a cellular immune response against HAV antigens which remained trapped in the corneal stroma under Bowman’s membrane.

If the infiltrates involve the visual axis, photophobia and visual acuity loss can occur and, if untreated, they resolve within a period that can vary between weeks and months. Even though said infiltrates are sensitive to the use of topical corticosteroids, the improvement seems to be temporary and does not affect the long-term length of the process.

Bacterian overinfection is not frequent but it could occur. The most frequently involved passive genes are gram-positive cocci such as Streptococcus pyogenes. Overinfection is particularly severe in children and could go as far as causing amblyopia.

unilateral condition, although it can become bilateral in up to 70% of cases. The most frequent symptoms are tearing, foreign body feeling and photophobia. The most frequent signs are predominantly bulbar conjunctival reddening (Fig. 1A) and in tharsal conjunctivitis the appearance of follicular reaction (more importantly in inferior tharsal conjunctivitis, Fig. 1B and C), conjunctival chemosis, petechiae and even full subconjunctival hemorrhages. The duration of the inflammation varies between 1 and 4 weeks.

The appearance of pseudomembranes (Fig. 2) is a frequent complication in patients with EKC, above all if the infection is caused by serotypes 8, 19 and 37. Pseudomembranes are clots of exudates firmly adhered to the upper and lower tharsal conjunctivae. It is possible to separate them from the

Fig. 1 – Bulbar conjunctival hyperemia (A) and follicle-petechial reaction in the upper (B) and lower (C) bulbar conjunctiva in a patient with epidemic keratoconjunctivitis.

Fig. 2 – Pseudomembranes in superior tharsal conjunctiva in patients with epidemic keratoconjunctivitis. Photography courtesy of Dr. Mateos Sánchez.

Fig. 3 – Subepithelial infiltrates which appeared 2 weeks after the resolution of epidemic keratoconjunctivitis.
Pharyngoconjunctival fever

PCF is a well-described syndrome attributed to HAV subgenotype B, particularly serotype 21 which causes small outbreaks, mainly among children. Outbreaks are frequent in schools, kindergartens and summer camps.

PCF courses with an acute onset comprising fever, pharyngitis, rinitis, cervical adenopathies and bulbar and palpebral conjunctivitis with slight-moderate follicular reaction. The duration of the condition is of 3–5 days. Ocular inflammation also begins in one eye and generally becomes bilateral in the course of the disease. Bacterial overinfection and ocular complications are much less frequent than in EKC.

The main sources of infection associated to PCF are contaminated waters of swimming pools and water reservoirs.21

Diagnostic

The diagnosis of these diseases is made usually on the basis of anamnensis and on the patient clinical findings. Differential diagnosis should include the following pathological processes:

- Allergic conjunctivitis. Symptoms are generally similar in the early stages. However, allergic conjunctivitis is more frequently bilateral and symmetrical in addition to subacute or chronic course. These patients generally exhibit papillary conjunctival reactions which is more intense in the upper tharsal conjunctiva. Itching is the most characteristic symptoms of allergic conjunctivitis,22 whereas the foreign body feeling would indicate adenoviral origin.

- Herpetic conjunctivitis. These patients exhibit typically unilateral symptoms and complain more frequently about pain. Occasionally, the characteristic blisters can be seen in the conjunctiva and mainly in the skin of the eyelids. Herpetic conjunctivitis could include bacterial overinfection with greater frequency than adenoviral conjunctivitis. Herpetic conjunctivitis has a self-limited course of 8–9 days.14

- Chlamydia inclusion conjunctivitis. This disease exhibits larger follicle sizes, mainly in the inferior sac fundus. In addition, these patients may refer Chlamydia genital-urinary infection history in themselves or their sexual partners.

A severity evaluation could be necessary to perform clinical studies or essays. The heterogeneous nature of the evaluation of conjunctivitis severity is a significant problem when comparing studies on this disease or preparing meta-analysis. For this reason, it is proposed that future studies apply the symptoms and signs scales proposed by the International Ocular Inflammation Society (Tables 1 and 2).23

Even though the diagnosis of AKC continues to be mainly clinical, tests are available in the market to confirm the adenoviral etiology of conjunctivitis. RPS (rapid pathogen screening) Adeno Detect is approved by the FDA for use in ophthalmology practices.24 This test is based on the principles of lateral flow immunochromatography which detects a region of the virus which is very well preserved among the various serotypes.25

<table>
<thead>
<tr>
<th>Table 1 – Symptoms scale of the International Ocular Inflammation Society.</th>
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<tbody>
<tr>
<td>Foreign body feeling</td>
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<tr>
<td>Photophobia</td>
</tr>
<tr>
<td>Tearing</td>
</tr>
<tr>
<td>Itching</td>
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and provides results in only 10 min. In addition it has demonstrated a sensitivity of 88% and a specificity of 91% vis-à-vis adenovirus cell cultures as well as a sensitivity of 89% and specificity of 94% vis-à-vis PCR.26 Its use has been recommended in primary health care so that a positive result could justify conservative management of conjunctivitis by primary health care physicians.26 Udeh et al. found that the systematic use of this test could reduce costs derived from the inadequate use of antibiotics in patients with EKC in 71.30 US dollars per patient.27

For epidemiological studies, the tests considered as gold standard continued to be cell cultures and PCR. HAV cell cultures, traditionally considered as gold standard for diagnosis, are laborious and take 3 weeks to produce results. In addition, culture results may vary depending on how the sample and the seeding are performed as well as on the identification of the cytopathic effects by technicians.28 For this reason, the use of HAV cell cultures is being substituted by new PCR techniques which are able to amplify small amounts of a viral DNA with great sensitivity and without losing specificity, to the extent that nowadays said techniques are considered to be the new gold standard.26 PCR-RFLP (restriction fragment length polymorphism) detects HAV serotypes in 24–48 h, and RT PCR (real time PCR) provides information about the rate of virus proliferation and the number of copies present at a given point in time.14

Treatment

To this date there is no specific drug against HAV replication. There is a search for molecules active against HAV replication without adverse effects.29 Some candidates that have exhibited benefits in these areas are zalcitabine,30 saniludine,29 cidofovir,31 interferon beta,29,32,33 antiosteoontine peptide29 and N-chlorotaurine,34 although randomized clinical trials must be carried out to confirm the efficacy and safety of these molecules in the treatment of AKC.

AKC is a self-limited disease that exhibits complete resolution within 3 weeks in most cases. At this time, AKC treatment is focused on managing patient symptoms and avoiding the appearance of complications while the patient immune system resolves the infection. To this end, the following treatments are available.

Conservative measures

Even though there are no trials confirming the usefulness of these measures, the use of cold packs and artificial tears
### Table 2 – Signs scale of the International Ocular Inflammation Society.

<table>
<thead>
<tr>
<th>Characteristics of membranes and pseudomembranes</th>
<th>0: none</th>
<th>1: present in one sac fundus</th>
<th>2: present in both sac fundus</th>
<th>3: present beyond the sac fundus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depth of erosion-ulceration</td>
<td>0: none</td>
<td>1: superficial epithelium</td>
<td>2: deep epithelium</td>
<td>3: tenon and/or sclera</td>
</tr>
<tr>
<td>Type of staining (rose Bengal or lissamine green)</td>
<td>0: none</td>
<td>1: micro- or macro-dots</td>
<td>2: filliform</td>
<td>3: patch shapes</td>
</tr>
<tr>
<td>Extension of staining (rose Bengal or lissamine green)</td>
<td>0: none</td>
<td>1: under 25% of conjunctival surface</td>
<td>2: between 25% and 50% of conjunctival surface</td>
<td>3: over 50% of conjunctival surface</td>
</tr>
<tr>
<td>Palpebral conjunctiva</td>
<td>0: smooth and uniform appearance</td>
<td>1: slight (localized formation of papillas or follicles under 1 mm diameter, without fluorescein staining at the peak)</td>
<td>2: moderate (diffuse formation of papillas or follicles under 1 mm diameter, with or without fluorescein staining at the peak)</td>
<td>3: severe (abundant papilla or follicles over 1 mm diameter, with or without fluorescein staining at the peak)</td>
</tr>
<tr>
<td>Secondary corneal involvement</td>
<td>0: none</td>
<td>1: under 25% of corneal surface</td>
<td>2: between 25% and 50% of corneal surface</td>
<td>3: over 50% of corneal surface</td>
</tr>
</tbody>
</table>

**Conjunctival hyperemia (bulbar/palpebral)**
- 0: none
- 1: slight vascular congestion
- 2: moderate vascular congestion
- 3: intense vascular congestion

**Conjunctival edema**
- 0: without edema
- 1: slight (edema in one segment of the bulbar conjunctiva)
- 2: moderate (uniform and diffuse edema throughout the bulbar conjunctiva)
- 3: severe (conjunctival chemosis with profusion of conjunctiva outside of the palpebral slit)

**Palpebral edema**
- 0: without edema
- 1: slight (discrete swelling of the upper or lower eyelid without changes in the palpebral slit)
- 2: moderate (upper and/or lower eyelid swelling with diminished palpebral slit)
- 3: severe (swelling of both eyes it’s that causes partial or total closure of the palpebral slit)

**Secretion**
- 0: no secretion
- 1: slight (discrete sticky secretion limited to sac fundus, only visible with slit lamp)
- 2: moderate (secretion visible without slit lamp)
- 3: severe (abundant secretion which can produce adherence of both eyelids)

### Table 2 (Continued)

could provide efficient symptom relief with hardly any risk of adverse effects.

**Topical corticosteroids**

Rabbit studies have demonstrated that the use of topical corticosteroids could increase the replication rate of adenovirus in the conjunctiva and extend the duration of infection. On the other hand, the use of topical corticosteroids could worsen conjunctivitis if its etiology is herpetic and could increase the risk of bacterial overinfection. Accordingly, the use of topical corticosteroids should be restricted.

In accordance with the above, the use of topical corticosteroids should be restricted to complicated cases with pseudomembranes or subepithelial infiltrates, where it appears to be efficient. In what concerns infiltrates, the use of corticosteroids seems to significantly diminish its incidence during treatment although infiltrates can reappear when treatment is discontinued. However, the reestablishment of topical corticoid therapy is useful to achieve the elimination of infiltrates. Taking into account the adverse effects of topical corticoid therapy, treatment of subepithelial infiltrates should be reserved for cases where visual acuity is significantly impaired.

**Topical nonsteroid anti-inflammatories**

Rabbit studies have demonstrated that the use of topical ketorolac or diclofenac does not increase adenovirus replication in the conjunctiva or extend the infection duration and therefore could be a safe alternative for treating the symptoms of these patients.

**Topical antihistaminic and vasoconstrictors**

A randomized clinical trial carried out in Pakistan reported the usefulness of associating topical antihistamins such as nafiracine with topical vasoconstrictors such as feniracine to shorten EKC duration and improve symptoms in a statistically significant manner. However, due to the risk of local toxicity and hypersensitivity, the use thereof should not be considered safe in the presence of severe itching because the risks could offset said benefits.

**Topical cyclosporine A**

Rabbit studies have demonstrated that the use of 0.5% topical cyclosporine A in artificial tears and 2% in corn oil reduces the incidence of post adenoviral subepithelial infiltrates, extending at the same time the duration of the infection. A retrospective nonrandomized study in humans
demonstrated that the use of topical cyclosporine A does not increase the visual acuity in a statistically significant manner in patients with subepithelial infiltrates, although it did improve objective signs. A randomized clinical trial in humans demonstrated that the use of cyclosporine A in combination with cidofovir did not significantly diminish the incidence of subepithelial infiltrates in comparison with cidofovir on its own.

Considering the above results, topical cyclosporine A should be used only in patients with subepithelial infiltrates that produce significant visual acuity loss and do not respond to topical corticoid therapy.

**Povidone-iodine**

Povidone-iodine is a broad spectrum antiseptic. A phase 2 clinical trial with 6 patients found that the use of 0.4% topical povidone iodine in combination with 0.1% topical dexamethasone eradicated the secretion of virus in 5 patients on the fifth day of follow-up. However, a clinical trial carried out in children did not find differences in the rate of healing between those treated with 1.25% povidone iodine or with antibiotic. New randomized clinical trials are necessary to determine the actual efficacy and safety of povidone iodine treatments in patients with AKC.

**Topical antibiotic therapy**

The use of topical antibiotics to prevent bacterial overinfection should be reserved for high risk patients such as children.

**Excimer laser**

A recent series of cases has reported the usefulness of Excimer laser phototherapeutic keratectomy to improve best corrected visual acuity in patients with persistent subepithelial infiltrates secondary to AKC.

### Prophylaxis

As there is no efficient antiviral treatment against HAV, prophylaxis is essential to control the infections caused by this pathogen. Washing of hands and disinfection of instruments do not appear to be sufficient to control the propagation of AKC outbreaks. A prospective study demonstrated that the application of a hospital infection control protocol against adenovirus can diminish the incidence of epidemic outbreaks and isolated adenoviral conjunctivitis cases through a four-year period. Recently, Dart et al. demonstrated again that the application of an AKC identification and control protocol diminishes the incidence of hospital contagion.

The measures that have demonstrated to diminish the incidence of AKC contagion are summarized in Table 3.

### Conclusions

AKC is an ocular surface infection produced by multiple HAV serotypes, a DNA virus without envelope highly resistant to physical and chemical agents that is contaged through direct contact or fomites. The most frequent clinical syndromes are EKC and PCF. EKC gives rise to severe ocular surface inflammation which can be complicated with the formation of pseudomembranes or subepithelial infiltrates caused by cellular immune reaction against virus antigen remains trapped below Bowman’s membrane. The diagnosis is mainly clinic although the etiology can be confirmed by tests such as RPS Adeno Detector, cell culture or PCR. There is no efficient antiviral drug against HAV. Therefore, symptomatic treatment is recommended with conservative measures and topical nonsteroidal anti-inflammatory drugs. If complications arise the use of topical corticoid therapy could be indicated. Prevention is crucial to control the propagation of this infection.

### Conflict of interest

No conflict of interest has been declared by the authors.

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