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Review Article

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ADENOVIRUSES IN OPHTHALMOLOGY REVIEW

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ABSTRACT

Adenoviral conjunctivitis is a self-limited disease that usually heals itself spontaneously within 1-3 weeks. Treatment management has focused on cold application, lubrication and topical nonsteroidal antiinflammatory treatment, as effective antiviral therapy against human adenoviruses is not yet available. Topical steroid treatment is indicated for visually threatening complications. Late scarring can be treated with phototherapeutic keratectomy. Preventive approaches are also needed to control the spread of the disease. Regular hospital infection control practices have an important place in controlling adenovirus infection, with general measures such as hand washing and instrument sterilization. Advances in pathogen early recognition, tight commitment to hygiene rules and adenovirus control programs will significantly reduce community outbreaks.

KEYWORDS: Adenoviral conjunctivitis, nonsteroidal antiinflammatory.

INTRODUCTION

Adenoviruses are icosahedral, enveloped and double-stranded DNA viruses and cause a number of diseases such as conjunctivitis, gastroenteritis, hepatitis, myocarditis and pneumonia.[1] Adenoviruses are highly contagious organisms with different antigenic identifiers and over 50 known serotypes. The most common type of adenoviral eye involvement is epidemic keratoconjunctivitis (EKC) followed by pharyngoconjunctival fever (PCF). The appearance of all ocular surface involvement, including conjunctiva and corneal epithelium, is a distinctive feature of EKC. Pseudomembranous, symblepharon, and multifocal subepithelial infiltrates, which are seen in severe cases, may result in decreased visual acuity.[2-4] PCF is characterized by fever, pharyngitis, acute follicular conjunctivitis and preauricular lymphadenopathy. Also isolated adenoviral conjunctivitis can be seen without corneal or systemic involvement. Contact with hand eye contact, ocular secretions, aerosols, ophthalmic caregivers and ophthalmic devices are main routes of transmission.[5] Adenoviral conjunctivitis is a biphasic disease that begins with an infectious phase followed by an inflammatory phase. Viruses continue to shed in ocular secretions for up to 7-10 days from the onset of infection. The patient will continue to be infectious until 2-3 weeks.[6]

Adenoviruses are the most common cause of acute viral infections of the conjunctiva, affecting up to 75% of cases.[7] According to the data from the Japan national surveillance center, adenoviral conjunctivitis affects 1 million people every year.[8] Precise statistical data, prevalence and incidence values are not available because of the inability to access medical care or access to health facilities. According to the data of Germany; while most affected group is adults by disease, the disease is seen in all age groups and gender dominance is not observed.[9] Although EKC is generally observed between 20-40 years, PCF tends to be seen mostly in children.[10,11]

Adenoviruses are divided into 7 different species (A-G) and a number of serotypes according to their immunohistochemical properties, nucleic acid similarities, hexose and fiber protein lengths, biological properties and phylogenetic analyzes.[12,13] Adenoviral conjunctivitis may occur sporadically or epidemically throughout the year. The severity and prevalence of the disease is related to the serological subtype. Serotype 8, 9 and 17 (type D) were associated with EKC; serotype 3, 5, 7 and 11 (types B and C) PCF; serotype 1-11 (species B-E) is associated with isolated follicular conjunctivitis without sore throat and auricular lymphadenopathy.[14,15] According to the results of epidemiological studies in Japan, adenoviral conjunctivitis cases with serotype 3, 4 and 37 were found to increase with increasing air temperature.[16] Germany's data also support an increase in adenoviral conjunctivitis cases in hot weather.[10] Outbreaks of EKC are common in hospitals (especially in ophthalmology units),[17-19] intensive care units,[20,21] and care homes;[22] PCF outbreaks are more common in schools, nurseries and summer camps.[23]

Both the EKC and PCf tend to be more frequent in the environments where close relationships need to be demonstrated. Direct contact with ocular secretions is the most common route of transmission. The infection can also be transmitted through the tonometer used by the eye caregiver, the cover speculum, and the split lamp. In one study, the positivity rate of hand sweep of infected patients was 46%.[5] Although the risk of infection with a family-friendly contact infection is 10%, the risk is increased when the infection is prolonged.[24] Nasocomial EKC outbreaks are widespread especially in ophthalmology units; postponement of ophthalmologic surgery, early discharge after surgery and closure of the operating room for a while.[8]

Epidemic Keratoconjunctivitis (EKC)

At least 19 of the adenovirus serotype that is 60 or more can cause EKC. Serotypes 8,9 and 17 are the most common causes, and less frequent 2-5, 7, 9, 10, 11, 14, 16, 21 and 29 can lead to the EKC table. The incubation period varies from 4 to 24 days and the symptoms tend to last for 7 to 21 days. After the symptoms have cleared, the patient continues to be contagious for 10-14 days. The virus can not be detected by PCR analysis in ocular secretions before the onset of symptoms.[25] Although the first phase of the EKC is unilateral; has been shown to cause double-sided disease in up to 70% of cases.[11] Red and pink eyes, excessive watering, foreign body sensation and photophobia are the most common symptoms. In severe cases, the patient may complain of decreased visual acuity associated with orbital and periorbital pain.

They are usually have recent eye examinations, affected family members or professional contacts in their anamnesis. Sometimes there may be flu-like symptoms, fever, vomiting, diarrhea, myalgia and difficult breathing before infection. Ocular findings are marked conjunctival redness, chemosis, tarsal follicular reaction, petechiae or subconjunctival hemorrhage.

Pharyngoconjunctival Fever (PFC)

PFC is most often caused by adenovirus serotype 3 and less frequently by serotypes 2, 4, 7, and 14. Serotypes 1, 5, 6, 8, 11 and 19 are the cause of sporadic outbreaks.[26,27] It is an acute and highly contagious disease accompanied by fever, pharyngitis, rhinitis, acute follicular conjunctivitis, and sensitive preauricular lymphadenopathy. Ocular inflammation is unilaterally starts and affects other eye within 1-3 days. The most common ocular findings are swelling and scaling of eyelids, epifora, conjunctival injection, conjunctival chemosis, follicular and papillary reaction, and subconductival haemorrhage. Contamination pathway is direct contact with droplet inhalation and ocular secretions. Although the incubation period varies between 5-12 days, the symptoms end within 3-5 days, limiting themselves and often without causing any complications.

Complications

Pseudomembranes containing a fibrin-rich exudate lacking blood vessels and lymphatics adhering to the upper and lower tarsal conjunctiva are more common in EKC cases and have been shown to be associated with adenovirus serotypes 8,19 and 37.[28] Unlike the true membranes, pseudomembranes can be separated without damaging the underlying epithelium, thus leading to little or no bleeding. Although pseudomembranes are generally observed in EKC cases, true membranes can also be observed according to the degree of the disease and the intensity of inflammation. Removal of true membranes leads to bleeding, leaving it in situ leads to subepithelial fibrosis and symblepharon formation.[29]

Another common complication observed in EKC cases is multifocal subepithelial infiltrates, which are pathognomonic for adenoviral infections. It has been shown in up to 50% of patients and has been shown to occur more frequently with serotype 8.[29] These infiltrates are a type of cellular immunological response to viral antigens stored in the corneal stroma beneath the bowman's membrane.[30] In vivo confocal microscopy study showing the clinical course of the EKC has shown that dendritic cells at the 1 st stage of diffuse epithelial keratitis are associated with subepithelial bowman membrane level accumulation. During the second week of focal epithelial keratitis, it has been shown that the hyperreflective basal cell clusters on dendritic cells are surrounded by a complex network of leukocytes. There is a hyperreflective layer of cells on the subepithelial infiltrate area in the anterior stroma.[31] The reduction in corneal sensitivity seen in the early phase of the disease probably improves on average of 8.5 days.[32]

Disease Progression and Treatment

Subepithelial infiltrates persist for weeks to years. These can cause visual impairment if they involve the visual axis. Most of these infiltrates heal spontaneously without scarring. Although topical corticosteroids shorten the healing time of infiltrates, there is no effect on long-term outcomes.[33] It has been shown that phototherapeutic keratectomy treatment combined with low dose mitomycin has a positive effect on photophobia, visual acuity and contrast sensitivity in the treatment of persistent corneal opacities developing as a result of EKC.[34]

Adenoviral conjunctivitis is usually a self-limited disease which results in complete recovery within about 3 weeks. Conservative approaches such as artificial tears and cold application provide symptomatic relief without any side effects. Topical antibiotics are used to prevent or treat bacterial superinfection.[35] The use of topical antihistamines and vasoconstrictors may also reduce the duration of the disease and complaints related to the disease, but there is also a risk of local toxicity.[36] Topical steroid use is controversial. Topical steroids are generally preferred in the acute phase of the disease and the effect is transient. The use of topical steroids in

animal studies has been shown to increase the adenovirus replication rate and therefore the disease recovery process is prolonged.[37-39] Steroid therapy should be restricted for complicated disease with visible pseudomembranes or subepithelial infiltrates with decreased visual acuity.[33,37] It has also been shown that topical nonsteroidal antiinflammatory use does not reduce adenovirus replication in animal models.[40] Because topical nonsteroidal antiinflammatory use has no effect on subepithelial infiltrates, it may be a safer alternative to steroid use for symptomatic relief.[41]

The effects of the virustatic agents trifluridine, vidarabine and ganciclovir on adenoviruses are limited, and the use of adenoviral conjunctivitis therapy is still controversial.[42-44] Topical ganciclovir experimentally reduces adenovirus burden,[42-45] but clinical studies have shown no effect on adenoviral conjunctivitis.[46] Significant antiviral activity of topical cidofovir against adenoviruses has been demonstrated in experimental studies and in animal models.[47-50] Topical cidofovir administration reduces the duration of the disease by reducing viral titers and is also effective in the prophylaxis of adenovirus.[51] In a clinical trial comparing the rate of symptomatic treatment of acute adenoviral conjunctivitis, combining topical cidofovir alone or with topical cyclosporine has not been shown to be a superior superiority of the disease to the disease.[52,53] It has been shown in animal models that the antiadenoviral effect of 2'3'-dideoxycytidine, an antiviral agent, is higher than that of sidofovir.[54]

Interferons are proteins that are responsible for stopping viral spread in response to viral infection and released from the cells. In some studies, topical interferon beta treatment has been shown to be effective in reducing the duration and complications of the disease.[55-57] Interferon gamma therapy can also be used as a treatment option because of its antiadenoviral activity.[58-60] Therapeutic effect of interferon alpha treatment has not been demonstrated.[61-63] Anti adenoviral activity is shown in animal models of topical immunoglobulin treatment; there is no human study.[64]

Povidone-iodine is a broad-spectrum antiseptic and, despite high activity against free adenoviruses, its activity against intracellular adenovirus particles in infected cells is poor.[65,66] The combination of topical povidone-iodine and dexamethasone has been shown to reduce viral secretion and disease duration.[67,68] Topical steroids provide symptomatic relief; topical povidone-iodine also kills viruses that shed in tears, thereby reducing the risk of spreading the disease. In a recent study, it has been shown that conjunctival washing with 2.5% povidone-iodine in infants is effective in the treatment of adenoviral conjunctivitis.[69]

Unlike acute disease, topical steroids have been shown to reduce adenovirus-associated subepithelial infiltrates.[33,70,71] However, this condition recurs after the cessation of treatment. This does not only lead to treatment dependency; at the same time steroids may result in cataracts and increased intraocular pressure. Cyclosporins used as an alternative to steroids do not provide symptomatic relief in the acute phase of the disease and have no activity on the natural course of the disease but are used in the treatment of subepithelial infiltrates following adenoviral conjunctivitis.[52,53] Topical cyclosporine treatment, varying between 0.05% and 2%, reduces subepithelial infiltrates and associated foreign body sensations and visual complaints.[72-75] Although topical cyclosporine treatment increases viral efflux in an animal study and therefore poses a risk for local epidemics, it is still a relatively safe treatment.[76] Phototherapeutic keratectomy therapy combined with low dose mitomycin C should be reserved for chronic subepithelial infiltrates with severe visual disturbances and treatment has shown positive effects on photophobia, visual acuity and contrast sensitivity.[77,78]

Since adenovirus conjunctivitis and complications are not effective treatments, strict sterilization of the hands and instruments is essential controlling the spread of the infection.[10,11,80] Because adenoviruses are resistant to many antiseptics, the type and amount of antiseptic used is important.[81] Human adenoviruses are resistant to dryness and can survive significant periods of time outside the human body. Plastic and metal surfaces have been shown to produce infectious concentrations even 28 days after settlement.[82,83] Simply deleting surfaces with general disinfectants such as isopropyl alcohol or hydrogen peroxide is ineffective against adenoviruses.[81,84] When adenovirus is suspected, it is recommended to be taken into an isolated contamination room and all surfaces and instruments should be disinfected with 70% ethyl alcohol and 1/10 of bleach after examination.[81,85] Disinfection should be done starting from the cleaning of organic matter.[81] The use of gloves, single-use tonometer heads and disposable eye drops can reduce transmission.[5,80] Patients should be informed about the course of the disease when they arrive in the acute phase of the disease and be cautious at the point of call for control at this time that they are contagious.

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