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HUMAN ADENOVIRUS: VIRAL PATHOGEN WITH INCREASING IMPORTANCE

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The aim of this review is to describe the biology of human adenovirus (HAdV), the clinical and epidemiological characteristics of adenoviral epidemic keratoconjunctivitis and to present a practical update on its diagnosis, treatment, and prophylaxis. There are two well-defined adenoviral keratoconjunctivitis clinical syndromes: epidemic keratoconjunctivitis (EKC) and pharyngoconjunctival fever (PCF), which are caused by different HAdV serotypes. The exact incidence of adenoviral conjunctivitis is still poorly known. However, cases are more frequent during warmer months. The virus is endemic in the general population, and frequently causes severe disease in immunocompromised patients, especially the pediatric patients. Contagion is possible through direct contact or fomites, and the virus is extremely resistant to different physical and chemical agents. The clinical signs or symptoms of conjunctival infection are 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, antigen detection, polymerase chain reaction or immunochromatography. Multiple treatments have been tried for this disease, but none of them seem to be completely effective. Prevention is the most reliable and recommended strategy to control this contagious infection.

Keywords: human adenovirus (HAdV), serogroups, epidemic keratoconjunctivitis (EKC), pharyngoconjunctival fever (PCF)

Introduction

Human adenoviruses (HAdVs) are classified in the genus *Mastadenovirus,* which contains seven known HAdV species HAdV-A to HAdV-G [1–3]. In 1953, adenoviruses were first isolated by Rowe and colleagues while studying the growth of polioviruses in adenoidal tissue [4]. During this study, a transmissible agent was identified which was capable of causing cytopathic changes in tissues in the absence of poliovirus. Traditionally, the HAdV species were classified by hemagglutination and serum neutralization reactions into different serotypes [1, 2]. Today, there have been reported 67 HAdV types. However, according to the genebank (http://hadvwg.gmu.edu/) [3] for human adenovirus genotype classification, HAdV type 68 – belonging to subgroup B – has been reported in 2012. The discovery and division of the HAdV types 52–68 are based on the genomic sequencing and bioinformatic analysis and different from the pre-existing 51 HAdV serotypes identified by traditional serological methods in composition and pathogenicity [1]. An additional serotype 52 constitutes a new HAdV species and has recently been reported after genomic sequencing and phylogenetic analysis of an isolate in the U.S. [5, 6]. New HAdV types have since been identified by several authors based on genomic data, including several emerging and recombinant viruses [7–14]. Most recently, a primate adenovirus from New World monkeys was detected which crossed the species barrier to infect humans [15, 16]. The majority of new HAdV types are homologous recombination within the same subgenus, and as a result, certain new serotypes acquire different pathogenicities. Recombination is a common evolutionary way for HAdV; however, the mechanism of recombination and the potential hazards to human beings remain unknown [1].

Adenoviruses can cause an array of clinical diseases, including conjunctivitis, gastroenteritis, hepatitis, myocarditis, and pneumonia *(Table 1)*. Most of these occur in children younger than the age of 5 years and are generally self-limiting illnesses. They commonly present with mild gastrointestinal symptoms, respiratory symptoms,

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Table 1. Adenovirus serotypes and associated clinical diseases [5–7, 17, 34–37]

HAvD subgroup	Serotype	Type of infection
A	12, 18, 31	gastrointestinal, respiratory, urinary
B, type 1	**3, 7, 16, 21**	keratoconjunctivitis, gastrointestinal, respiratory, urinary
B, type 2	11, 14, 34, 35	gastrointestinal, respiratory, urinary
C	1, 2, 5, 6	respiratory, gastrointestinal including hepatitis, urinary
D	**8–10,13,15,17,19,20,22–30,32,33,36–39,42–49**	keratoconjunctivitis, gastrointestinal
E	**4**	keratoconjunctivitis, respiratory
F	40, 41	gastrointestinal
G	52	gastrointestinal

or a combination of both. Globally, 5–7% of respiratory tract infections in pediatric patients are ascribed to HadV [17–19].

Some serotypes, such as HAdV type 14, have been associated with severe and potentially fatal outbreaks of pneumonia in residential facilities and military bases [20]. Of the seven HAdV subgroups (A to G), subgroup A has been associated with the gastrointestinal tract [21, 22], while subgroups B and C are more common to the respiratory tract [21], though conjunctivitis outbreaks have been associated with HAdV type 3 (subgroup B-1, *Table 1*). HAdV subgroup D overwhelmingly causes conjunctivitis [21, 23, 24], and subgroup E is associated with respiratory and ocular infections, but more commonly in conjunctivitis [21]. Finally, subgroups F and G are the causative agents of gastroenteritis [17, 21].

Adenovirus: biology, classification, and associated diseases

Adenoviruses are non-enveloped double-stranded DNA viruses that can infect a variety of human tissues. They range in size from 65 to 80 nm in diameter. The virion is composed of a protein capsid, made up of 252 capsomeres, and a nucleoprotein core that contains the DNA viral genome (26–46 kbp long, containing 23–46 protein-coding genes) and internal proteins. The capsid has an icosohedral shape, consisting of 240 hexon components and 12 pentons per virus particle [25, 26]. Each penton contains a base plate with fiber. The length of the fibers varies among the different serotypes [27]. DNA homology within the HAdV subgroups ranges from 48% to 99%. HAdV subgroup C serotypes revealed the highest DNA homology (up to 99%) as compared to other HAdV subgroups. However, the DNA homology between HAdV subgroups is less than 20% [17].

There is a varying degree of oncogenicity among the HAdV serotypes. For instance, HAdV subgroup A types, such as HAdV type 12, are highly oncogenic [28–30] with the ability to induce tumors in new born rodents within 4 months. On the other hand, HAdV subgroup B are weakly oncogenic, and finally HAdV subgroups C, E, and F are not known to be oncogenic. However, it has been shown that the cells transformed by non-oncogenic HAdV can cause tumors in immunocompromised host, indicative of the host immune system rejecting those transformed by the non-oncogenic adenoviruses [31–33].

HAdV type 8 (HAdV-8) is a major causative agent of epidemic keratoconjunctivitis which is frequently associated with community, military, industrial, and nosocomial outbreaks. To date, HAdV-8A, B, E, and I have been found in Japan as variants of HAdV-8. In the recent time, two novel HAdV types causing nosocomial EKC were reported from Japan [38–40]. One of these has been misclassified as HAdV-8 in some cases because of its similarity to HAdV-8, according to neutralization test and phylogenetic analyses. However, the virus showed completely different restriction patterns from those of other published HAdV-8 genome types, revealing it is a novel serotype and is named as HAdV-54 [38].

Epidemic keratoconjunctivitis (EKC) is caused by a group of HAdVs of different serotypes that can also cause pharyngoconjunctival fever (PCF) and nonspecific follicular conjunctivitis. EKC is highly contagious, has a tendency to occur in epidemics, and has been reported worldwide such as epidemic outbreaks in hospitals, swimming pools, military bases, schools, and other community settings; in Asia, this disease is endemic [41–45]. In 1955, Jawetz et al. [25] were the first to attribute the etiology of EKC to the infection of ocular surface tissue caused by HAdV. EKC is one of the most common causes of acute conjunctivitis, with characteristic clinical features such as sudden onset of acute follicular conjunctivitis, with watery discharge, hyperemia, chemosis, and ipsilateral pre-auricular lymphadenopathy [46].

Epidemiology of epidemic keratoconjunctivitis (EKC)

EKC 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 most difficult to acquire precise statistical data. The actual prevalence and incidence of EKC in countries, such as

Germany, is well documented [41–44, 46–48]. EKC cases have to be reported to the medical authority in Germany. However, the prevalence and incidence of EKC at the international level are unknown. The infection is more common in adults, but all age groups can be affected with no specific gender affinity as has been reported by Adlhoch et al. [48]. Their analysis did not show a disproportionately affected gender or age group, but many infections were preceeded by exposure to ophthalmological facilities, communal facilities, or public places. Seasonal patterns of infection have been demonstrated in the general pediatric population. This depends upon the HAdV serotypes and the population groups exposed. EKC is caused mainly by HAdV-3 (in HAdV-B), HAdV-4 (in HAdV-E), and HAdV-8, HAdV-19, and HAdV-37 (in HAdV-D). Among these, HAdV-8, HAdV-19, and HAdV-37 cause more severe conjunctivitis than the others [49]. HAdV-37 was first isolated from patients with keratoconjunctivitis in 1976 in The Netherlands and was reported by De Jong et al. as a newly identified serotype [27]. In northern Japan, HAdV-37 has been isolated every year since 1977 [50] and has caused large epidemics of conjunctivitis in the last two decades [49]. EKC outbreaks have been mainly associated to serotypes 8, 19, and 37, whereas PCF cases have been related more with serotypes 3, 7, and 11 [17, 36, 47–49, 51].

Symptomatology and clinical signs of epidemic keratoconjunctivitis (EKC)

EKC patients may complain about flu-like symptoms, including fever, malaise, respiratory symptoms, nausea, vomiting, diarrhoea, and myalgia. Recent history of ophthalmological examination or exposure within the family or at work has been documented in most cases. The incubation period is 2–14 days, and the person may remain infectious for 10–14 days after the onset of the symptoms. The ocular symptoms are mainly sudden onset of irritation, soreness, red eye, photophobia, foreign body sensation, and excessive tearing. More severe cases may include ocular and periorbital pain and decreased visual acuity. Symptoms tend to last for 7–21 days [17, 46, 49, 51, 52]. Ipsilateral pre-auricular lymphadenopathy is one of the classic findings of EKC. Decreased visual acuity is rarely present; it is usually present only if there is corneal involvement. Other clinical signs may include swelling and erythema of the lid, conjunctival hyperemia, chemosis, follicular reaction, mainly in the lower palpebral conjunctiva (the earliest and most common sign), papillary hypertrophy, or subconjunctival and petechial hemorrhage. In severe cases, membranous and pseudomembranous conjunctivitis can be seen in one [46, 52].

One of the distinguishing features of EKC is corneal involvement, which is usually mild and transient. Corneal involvement has been well documented 3–4 days after symptom onset as diffuse, fine epithelial keratitis that stains with fluorescein. This keratitis can persist for 2–3 weeks and in few cases corneal epithelial defect may occur. A week after the onset, focal epithelial keratitis develops with central ulceration and irregular borders with gray-white dots. These epithelial changes are related to active viral infection. These lesions persist for 1 to 2 weeks. About 2 weeks post-onset, subepithelial infiltrates can appear beneath the focal epithelial lesions, persisting for weeks to years. These resolve spontaneously, usually without scarring. In rare cases, disciform keratitis or anterior uveitis can occur. There is no change in corneal sensation [46, 52]. Bacterial superinfection is not frequent but could occur; mostly involved are gram-positive cocci such as *Streptococcus pyogenes*. Bacterial superinfection is particularly severe in pediatric patients and could lead to amblyopia [53].

Symptomatology and clinical signs of pharyngoconjunctival fever (PCF)

Pharyngoconjunctival fever (PCF) is a well-described syndrome attributed to HAdV subgroup B, particularly serotype 3 [53], which causes outbreaks, mainly among children. Outbreaks are frequent in schools, kindergartens, and summer camps. Acute onset of PCF comprises fever, pharyngitis, rhinitis, cervical adenopathies and bulbar and palpebral conjunctivitis with moderate follicular reaction which can last for 3–5 days. PCF associated ocular inflammation begins unilateral and generally becomes bilateral in the course of the disease. Bacterial superinfection 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 [46, 53, 54].

Immunology, transmission and spread of human adenovirus

Immune responses to adenovirus infection depend on various factors including the inoculation site, the HAdV serotype, and the antibody status of the host. HAdVs have several mechanisms for evading host immune responses. These include the inhibition of intrinsic cellular apoptosis in infected cells, inhibition of responses to interferon and tumor necrosis factor (TNF), and the prevention of MHC class I expression on cell surfaces [17–19, 55, 56].

Antibodies to adenovirus (mainly secretory IgA) are present in the upper respiratory tract within 3 days of infection. Approximately 7 days post-infection, antibodies can be detected in serum, and nasal secretions contain both secretory IgA and IgG [17, 18]. Antibodies are directed against the hexon (alpha component) of the viral capsid, which contains the antigenic component that is common to all mammalian adenoviruses [17, 19, 55, 56]. Type-specific neutralizing antibodies are produced in response to another hexon component as well as viral fibre antigens. These have been demonstrated 10 years after primary infection and might explain why re-infection with the same serotype is uncommon [17, 18].

There are three possible ways of HAdV interaction with the host cell:

- lytic infection (epithelial cells): the virus completes its multiplication cycle, producing cellular death and releasing new viruses, of which up to 5% are infectious;
- latent infection (lymphoid cells): only small amounts of virus are released, and the cellular death rate is offset by normal multiplication;
- oncogenic transformation: the HAdV DNA is included in the cellular genetic material and replicates inside it without producing new infectious virus.

Animal models of adenoviral pulmonary infection have shown histopathological changes that can be divided into two phases: the first with predominantly monocyte and macrophage infiltrates typical of non-specific, cytokine-mediated inflammation, whereas the second phase is characterized by predominantly T-lymphocyte infiltration [17, 57].

T-cell-mediated immunity seems to be of importance for recovery after acute HAdV infection, since immunocompromised individuals who lack effective cellular immunity are at a much higher risk of adenoviral infection. It has been suggested that both clinical and laboratory features of adenovirus infections are consistent with Th1 cell responses (production of TNF and interferon γ by T-cells) [17, 18]. Adenovirus-specific CD4+ lymphocytes can recognize conserved antigens across different adenovirus serotypes. Infection with one serotype can therefore produce T-cell-mediated immunity to infection with different serotypes. However, the neutralizing antibodies against HAdVs are serotype-specific [17–19]. The presence of adenovirus-specific CD4+ T-cells in most asymptomatic adults suggests that adenovirus-specific cellular responses are long lived [17, 58].

Diagnostics of epidemic keratoconjunctivitis (EKC)

The diagnosis of EKC is usually made on the basis of anamnesis and clinical findings. However, HAdV detection is traditionally performed by cell culture or antigen detection methods. Most HAdVs grow readily in cell culture and can be detected in various specimen types including nasopharyngeal, throat and conjunctival swabs, urine, cerebrospinal fluid (CSF), and stool. However, some types can take up to 4 weeks to isolate, and diarrheagenic types 40 and 41 of the subgroup F show difficulty to grow in routine cell culture. Direct antigen detection from clinical specimens may be used for acute infections, but provides markedly low sensitivity compared to culture. Less commonly, serology is used to detect a rise in adenovirus-specific antibodies following infection [2, 46, 59–61]. Due to the high mortality rates from invasive disease, individual adapted screening of urine stool and blood for adenovirus in high-risk patients using PCR technology might present a sensible diagnostic approach to detect acute infection much earlier [2, 46, 61, 62].

Differential diagnosis should include the following pathological processes:

- *allergic conjunctivitis:* symptoms are generally similar in the early stages, but allergic conjunctivitis is more frequently bilateral and symmetrical; itching is the most characteristic symptoms of allergic conjunctivitis, whereas the foreign body feeling would indicate adenoviral origin,
- *herpetic conjunctivitis:* typically unilateral symptoms and more frequently associated with pain; could include bacterial superinfection with greater frequency than adenoviral conjunctivitis; herpetic conjunctivitis has a self-limited course of 8–9 days,
- *Chlamydia inclusion conjunctivitis:* exhibits larger follicle sizes, mainly in the inferior sac fundus; patients may refer *Chlamydia* genital-urinary infection history.

Differential diagnostic considerations

Besides EKC and PCF the following diagnoses should be considered in the differential diagnosis [17–19, 46] of:

1. acute follicular conjunctivitis:
   - acute trachoma
   - acute inclusion conjunctivitis
   - primary herpes simplex conjunctivitis
   - acute hemorrhagic conjunctivitis
   - infectious mononucleosis
   - neonatal inclusion conjunctivitis, etc.

2. subepithelial corneal opacities:
   - herpes simplex infection
   - herpes zoster infection
   - infectious mononucleosis
   - Epstein–Barr virus infection, etc.

Therapy of epidemic keratoconjunctivitis (EKC)

EKC is a self-limited disease that exhibits complete resolution within 3 weeks in most cases. To date, there is no causative therapy or specific drug against HAdV-associated diseases. EKC treatment is focused on managing patient symptoms and avoiding the appearance of complications while the patient immune system resolves the infection. However, the following treatments are available: some molecular compounds and cyctokines which are active against HAdV replication without adverse effects exhibited benefits: zalcitabine, sanilbudine, cidofovir, interferon beta, antiosteopontine peptide and N-chlorotaurine, although there is lack of randomized clinical trials of EKC [63–70].

Animal studies have demonstrated that the use of topical corticosteroids could increase the replication rate of HAdV in the conjunctiva and prolong the duration of infection. However, the use of topical corticosteroids should be restricted to complicated cases with pseudomembranes or subepithelial infiltrates, in cases where visual acuity could be impaired significantly [63–67, 71, 72].

Randomized clinical trial in humans demonstrated that the use of topical cyclosporine A in combination with cidofovir did not significantly diminish the incidence of subepithelial infiltrates in comparison with cidofovir on its own. Topical cyclosporine A should only be considered in patients with subepithelial infiltrates that produce significant visual acuity loss and do not respond to topical corticoid therapy [73, 74]. One of the ophthalmic broad spectrum antiseptics is povidone-iodine. 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 [75]. The use of topical antibiotics to prevent bacterial superinfection should be reserved for high-risk pediatric patients [73, 75].

Prevention and infection control/prophylaxis

As there is no efficient antiviral treatment against HAdV, 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 EKC outbreaks [44, 46, 76, 77]. 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 [46, 78]. Recently, Dart et al. [79] demonstrated again that the application of an EKC identification and control protocol diminishes the incidence of hospital contagion.

Current and future utilities: therapeutic use of adenoviruses

Vector-based utility of adenovirus has been demonstrated for gene therapy and vaccine applications although some limitations due to adenovirus have to be overcome: modification of the virus capsid, of the ligands, administration routes, and the use of genome modified adenovirus or development of chimeric or alternative serotype adenovirus [80]. Oncolytic adenoviruses have been generated as vectors and present a new modality to treat cancer. In 2005, the first oncolytic adenovirus was approved for the treatment of head-and-neck cancer by the Chinese authority. The vectors demonstrated modest anti-tumor effect when applied as a single agent; their efficacy improved when they were combined with another modality, including vector design, delivery techniques, and supplemental therapy [81, 82].

Summary

EKC is an ocular surface infection produced by diverse HAdV 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. The diagnosis is mainly clinical although the etiology can be confirmed by different diagnostic approaches, such as cell culture, antigen detection, and PCR. There is no efficient antiviral drug against HAdV. Therefore, symptomatic treatment is recommended with conservative measures and topical nonsteroid anti-inflammatory drugs. If complications arise, the use of topical corticoid therapy could be indicated. Prevention is crucial to control the propagation of this adenoviral infection.

Conflict of interest

No conflict of interest has been declared by the author.

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