Acute Hemorrhagic Conjunctivitis-A Brief Review

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Abstract

Acute hemorrhagic conjunctivitis (AHC) is a highly contagious eye disease. It is caused mainly by enterovirus 70 (EV70) and coxsackievirus A24 variant (CA24v). Using molecular methods can be helpful in rapid and specific viral strain identification. AHC's clinical features include: ocular soreness and itching, photophobia, foreign body sensation, and etc. AHC usually spans 2-3 weeks, and there are no drugs or vaccines for its prevention. Since AHC is highly contagious, appropriate infection prevention and control policies are quite important topics in public health. There have been several outbreaks in Taiwan since 1970, and it reappeared in October 2007. Proper disease control strategies enabled this outbreak to end quickly in one month. This review discusses topics in epidemiology and microbiology, laboratory diagnosis, clinical presentation, and prevention methods, with the objective to serve as a helpful reference for AHC control in the future.

Key Words：Acute hemorrhagic conjunctivitis, Taiwan, Outbreak

Introduction

Better known as "Pink Eyes,"acute hemorrhagic conjunctivitis (AHC) is an

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epidemic viral infection of the eyes. It was first described in Ghana in 1969. Humid coastal areas with high population density are major epidemic sites. Enterovirus 70 (EV70) and coxsackievirus A24 variant (CA24v) are highly contagious enteroviruses that cause AHC. In addition, several serotypes of adenovirus are also associated with it. EV70 appeared for the first time in 1969, and spread to almost the whole world. CA24v is an antigenic variant of coxsackievirus, and was isolated in Singapore in 1970 for the first time. Unlike EV70, CA24v had not been isolated outside Southeast Asia and India until 1986〔1,2〕.

AHC symptoms usually occur in both eyes, characterized by sudden onset of ocular pain, itching, lid edema and profuse excretion. Patients are usually automatically cured after two-three weeks〔3〕. Fomite-hand-eye contact is the major mode of transmission, and the virus spreads rapidly especially among family members. Due to its extremely contagious character, AHC can influence the local economy with a severe outbreak〔4〕. Therefore, prevention methods should be proposed to target high-risk groups.

Epidemiology and Microbiology

AHC first occurred in 1969 in Ghana, West Africa.. It spread throughout West Africa and reached North Africa in 1970. There were also some small-scale outbreaks in Indonesia (Djakarta and Bali) and Vietnam between 1969 and 1970. During the 1970s, AHC affected all of Southeast Asia and extended to India (Bombay, Calcutta), Japan, the Middle East (Bahrain and Saudi Arabia), and Europe (London, Rotterdam, Moscow, Yugoslavia). It affected Taiwan and Singapore in the mid-1970s〔1〕.

The disease was first reported in the Western Hemisphere in 1981, and

then spread throughout South America, Central America and the United States〔2〕. It has since become one of the most common eye infections in the world, with the possibility of a large-scale pandemic outbreak. From the perspectives of epidemiology and microbiology, the following section will explore AHC cases in different countries.

1. AHC in Taiwan

In the early 1970s, both Ad 11 and EV70 were isolated in an outbreak in Taiwan, but these two viruses could not be distinguished clinically〔5〕. During the Asian pandemic of 1980-1981, Ad 8 and EV70 were isolated from patients in the Kaohsiung area. Of 53 cases of AHC, EV70 isolation rate (15.1%) was higher then Ad8. From Sapporo cases in the same period, EV70 isolation rate was 40% in 60 cases〔6〕. Serological evidence showed that prior to the 1981 outbreak, an average of 34.0% EV70 antibody in serum among Taiwanese population, but only 5.3% CA24v antibody. It indicated that EV70 had been prevalent since the introduction in 1971, but CA24v had not endemically persisted before 1985, the first outbreak of CA24v in Taiwan〔7〕. From 38 Kaohsiung cases isolated between 1983 to 1984, 76.3% was EV70, others were Ad 4、Ad 8、Ad 3 and Ad 11 in order. None of CA24v was found〔8〕.

In October 1985, AHC occurred in Kaohsiung City, and it was the first outbreak caused by CA24v in Taiwan〔9〕. It ended quickly because of cooler weather. However, outbreaks were reported again in many areas of southern and central Taiwan in May 1986. Later, large numbers of cases occurred in Taipei City in June and July. Chou et al〔9〕 investigated some cases in Taipei, and found that since males may be more socially active than females, they introduced the illness into the households more often. Furthermore, behavior in younger children, such as poor personal hygiene, may increase the secondary

transmission rate after the initial infection

In 1985 to 1989, there were several AHC outbreaks caused by CA24v. It is known that the gene mutation rate is higher in the RNA virus than in the DNA virus. The mutation accumulation of CA24v may influence the antigenicities, pathogenicities, and etc. In order to know the phylogenetic relationship and the transmission route of CA24v, Lin et al〔7,10〕, compared the nucleotide sequences of virus-encoded proteinase 3C region ($3C^{pro}$, 549 nucleotides) from the 19 isolates of the four outbreaks in Taiwan(1985,1986,1988,1989), along with with the prototype strain (EH24/70) from Singapore, four isolates from Japan, and two isolates from Hong Kong. The results showed that the Taiwan and Japan isolates from 1985 to 1986 were closely related, and the 1988-1989 Taiwan and 1989 Japan isolates belonged to the same lineage. It was clear that the 19 Taiwan isolates had diverged into two groups because of discontinuous introductions of CA24v since its first appearance in Taiwan. Besides, $3C^{pro}$ nucleotide differences were found between the prototype and 1985-1986 isolates, and there were three additional amino acid changes in isolates after 1988. Since clinical symptoms in 1985-1986 were more severe than those in 1988-1989 patients, the amino acid substitution might relate to the clinical symptoms〔7〕.

In 1990 and 1994, AHC caused by CA24v reappeared in Taiwan. To analyze the genetic diversity, the entire CA24v $3C^{pro}$ sequence (from 7 Taiwanese strains, 1 Japanese strain and 2 Thai strains) was used for alignment. There were nucleotide differences between these 10 strains and the prototype strain, EH24/70. Analyzing $3C^{pro}$ sequence of 71 strains in 1970-1994 worldwide, the nucleotide sequence homologies were 88-100%. Phylogenetic analysis shows 3 genotypes and 6 clusters of genotype III. Isolates from Taiwan

obtained in 1985/1986, 1988/1989 and 1990-1994 were classified into genotype III Cluster 1,5, and 6, respectively〔11〕.

In October 2007, there was an AHC outbreak in Taiwan. It spread around in Keelung City, Taipei City, Taipei County, Yunlin County and Jiayi County. Patient samples had been analyzed by Taiwan's CDC National Libratory, and the results demonstrated that CA24v was the pathogen in this outbreak〔3〕.

2. AHC in India

In 1971-1972, the first piece of serologic evidence of EV70 infection in India came from Bombay (western India). During an epidemic in north India in 1981, EV70 prototype-like strain was isolated from Delhi, and antigen-positive cases were found by immunofluorescence in Chandigarh. Later, a prime-type EV70 isolate was obtained from Pune (western India) in 1991. During the interval of 1986-1991, CA24v was circulating as a cause of AHC in India〔12〕.

During the rainy season(August and September) of 1996, an AHC outbreak occurred in Delhi. Maitreyi et al〔12〕 conducted a study to identify the etiologic agent by the modified centrifugation-enhanced viral culture technique, immunofluorescence, neutralization tests, and PCR. The results indicated that EV70 strain reemerged as the AHC pathogen.

3. AHC in South Korea

During 1970-2000, several large outbreaks of AHC have occurred in South Korean. Scientists tried to isolate the virus in 1983, 1987 and 1990; most of them were Ad and EV70. In the summer of 2002, a nationwide outbreak of AHC occurred in South Korea and CA24v was determined to be the pathogen for the first time. There were 98.1% to 100% homologous in the nucleotide sequences of CA24v $3C^{pro}$ region among the 14 CA24v isolates. The phylogenetic analysis showed that the Korean CA24v isolates clustered into a

lineage distinct from those in the previous outbreaks in other Asian countries, such as Singapore, Taiwan, Hong Kong, which had been attributed to CA24v〔13〕.

4. AHC in American Samoa

American Samoa includes the main island of Tutuila and several off-shore islands. These islands experienced an epidemic of AHC caused by EV70 in 1981-1982. The overall attack rate was estimated to be 68%〔14〕. In the summer of 1986, AHC caused by CA24v affected about 47% of the population in Samoa. It was the first CA24v induced AHC outbreak outside Southeast Asia and the India subcontinent. When signs and symptoms were compared between these two outbreaks, EV70 was associated with more severe conjunctival hemorrhage than CA24v. However, upper respiratory and systemic symptoms were more common in AHC caused by CA24v. Age and type of household seemed to be main factors in disease transmission. There were lower attack rates for children under 4 years and adults greater than 50 years. The infection rate for traditional households was much higher than that in government households.〔2〕.

Between 1990-1991, an outbreak of AHC due to EV70 occurred in Samoa. It affected 58% of the population, and children aged 2-10 had higher rates than children of other ages. According to serologic data, this age group had significantly lower antibody titers than did older people, due to a lack of previous exposure to EV70 pathogens. Besides, women aged 21-40 years had higher rates than men did in the same age, 66% and 49% respectively. This is because females had closer contact with infected children.〔15〕.

5. AHC in Puerto Rico

Since 1981, three major epidemics of AHC have occurred on the

Caribbean islands. . In August 2003, a fourth epidemic caused by CA24v occurred in Puerto Rico. The number of reported cases increased weekly; it reached a peak after 6 weeks (mid-September) and returned to the baseline in late October. During this period, more than 51,000 cases were reported by physicians. The attack rate was higher among school-aged children (5-18 years), people living in crowded areas, and those inclose contacts with the infected people〔4〕.

6. AHC in Brazil

CA24v was the etiologic agent responsible for a large outbreak of AHC in Rio de Janeiro, Brazil, during April and May of 2004. More than 60,000 cases were officially reported to the state's public health authorities. Comparisons of partial VP1 gene sequence showed that it was more than 97% identical with the CA24v isolated in Korea and French Guiana from AHC outbreaks in 2002 and 2003. However, whether there was a direct route of disease dissemination among these countries remains unclear〔16〕.

Laboratory Diagnosis

In early research reports, confirming EV70 as an AHC pathogen was not easy because the virus cannot be isolated easily. Besides, antigen detection tests were not always successful, and serological tests were often not practical or unavailable at the outbreak sites. Anderson et al〔17〕, attempted to develop rapid diagnostic tests to detect EV70 antigens in clinical specimens and isolated material. Because it was difficult to make high-quality animal antiserum of EV70, they developed monoclonal antibodies (MAbs) of EV70. Experiment data showed that MAbs had type specificity and strain sensitivity in ELISA, IFA, and virus neutralization test. Wulff et al〔18〕, developed a method of

ELISA assay to capture IgM antibody. This method proved to be simple and relatively rapid to perform. Besides, only very small amount of serum is required.

In general, neutralization test is reliable in EV typing. Because of antigenic drift, recombination, or virus mixtures in the specimens, it is labor-intensive, time-consuming and may fail to identify the serotype of a clinical isolate. By using molecular methods, detection of EV types can be done more rapidly and specifically. Due to the molecular cloning technology development, nucleotide-sequencing analysis has become one of the precise methods. For example, nucleotide sequence of viral 5' nontranslated region (5'NTR) and the VP4-VP2 junction might be a diagnostic tool. But, the sequences in these regions do not always correlate with serotypes〔19,20〕. Because EV serotypes were defined by neutralization test, and viral VP1 region contains some important neutralization epitopes, VP1 sequence might correlate with serotyping. Oberste et al, demonstrated that the VP1 sequence appeared to correlate better with the serotype than does 5'NTR or the VP4-VP2 junction〔21〕.

Confirming CA24v as an AHC pathogen can be done by neutralization test. Besides, comparing the nucleotide sequences of $3C^{pro}$ sequence is also used in phylogenetic relationship analysis. For example, construction of a phylogenetic tree based on $3C^{pro}$ sequence revealed that CA24v could be divided into 3 genotypes and they were closely related to the transmission route of each outbreak. The evolution rate of CA24v is quite constant since its first emergence 〔7,10,11〕.

Clinical Presentation

In general, the clinical features of AHC due to EV70 and CA24v are indistinguishable. AHC is frequently bilateral and characterized by sudden onset of ocular pain and itching, photophobia, lid edema, foreign body sensation, profuse excretion and preauricular lymphadenopathy (PAL)〔1,2〕. Conjunctival inflammation is accompanied by subconjunctival hemorrhage (SCH) and follicular reaction in most cases. Researchers in Kaohsiung Medical University Hospital did an 18-year (1980-1997) analysis of epidemic viral conjunctivitis in southern Taiwan. CA24v induced the highest incidence of SCH, accounting for an overall of 54.9%. EV70 caused SCH in 44% of the infected patients. The incidence of PAL in conjunctivitis caused by CA24v was around 35%, and EV70 induced a lower incidence of 13.6%. Furthermore, the clinical symptoms changed from one break to another. SCH occurred in CA24v AHC with an incidence of 44.1% in the 1985-1986 outbreaks, 46.4% in the 1988-1989 outbreaks, 71.6% in the 1990-1991 outbreaks and 78.2% in the 1994 outbreaks〔22〕.

The incubation period is 1-7 days. It is infective 1-2 days before and after 14 days after symptom occurrence. Illness tends to resolve within 2-3 weeks. Corticosteroid can be used to reduce inflammation in clinical treatments〔3〕.

Mode of Transmission

Conjunctivitis may be bacterial, viral or chlamydial. AHC is mainly caused by enteroviruses and adenoviruses. Fomites-hand-eye contact is the major mode of transmission. High-risk groups are school-aged children, people living in crowded areas, and family members of the infected people due to close contact with them.

Prevention and Control

There are no drugs or vaccines for AHC prevention. Since patients who rub their eyes often contaminate their hands and cross-reaction may occur through contaminated hands and instruments, the best prevention way is caring about personal and healthcare workers' hygiene. Recommended prevention methods include: encourage correct and frequent hand washing, avoid rubbing eyes, avoiding sharing towels, makeup, and other personal items. The following are some infection control principles〔3,23〕:

1. Correct Hand Washing Steps

   Hand washing is most important for disease control. Here are the recommended steps for correct hand washing:

   (1)Wet hands with clean and running water.

   (2)Apply soap or cleanser, then rub the palms against each other for at least 20 seconds

   (3)Rinse off soap thoroughly with running water

   (4)Rinse the tap and turn it off

   (5)Dry hands by clean paper towels or handkerchiefs

2. Pay Attention to Healthcare Workers' Hygiene

   Healthcare workers contact patients directly, so their own personal hygiene is quite important. Patients who rub their eyes often contaminate hands, and the organism may transfer to the healthcare workers. It is necessary to wash hands immediately before and after performing an eye examination. Besides, sterilizing equipments after use on patients is important.

   In 2006, an epidemic keratoconjunctivitis outbreak occurred among clients of a regional eye clinic in Australia. It was caused by adenoviruse 8. Investigation showed that using contaminated multi-dose vial of anesthetic

drops was the main cause of infection. The epidemic was brought under control when the clinic reduced the number of patients and used single-dose vials. Therefore, when using multi-dose vials, it is necessary to avoid eyedropper contact with eyelids and lashes. The best situation is to use single-dose vials〔24〕.

3. A Clean and Safe Healthcare Environment

Patients have a right to be cared for in a clean and safe environment. Hospital environments and clinical equipments need to be kept clean. Clinical waste dispossals must follow the standard procedures.

Conclusion

It has been about forty years since AHC first occurred in 1969. Now, although AHC outbreaks are reported almost everywhere in the world, the disease rarely causes severe consequences, despite making infected people uncomfortable and influencing other people's health. Breakthroughs in molecular techniques lead to quicker pathogen confirmation and provide authorities and related staff speedier and more accurate information. Such progress will definitely help the adoption of appropriate infection-control policies. Furthermore, to bring the epidemic under control more quickly, it is most important to educate the people on the correct prevention concepts.

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