

# ACUTE HEMORRHAGIC CONJUNCTIVITIS OUTBREAK IN THAILAND, 1992

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**Abstract.** The 260 cases of acute hemorrhagic conjunctivitis seen at Siriraj Hospital during October to December, 1992 were studied. Evidence of coxsackie virus A24 variant (CA24v) infections was demonstrated in 76.8% of 95 cases. The isolation rates from conjunctival swabs and throat swabs were 68.2% and 32.8%, respectively. A four-fold rising titer of neutralizing antibody was shown in 59.5% of 42 cases. The disease was characterized by a short incubation period, sudden onset, a mild and self-limited course within 5 days without ocular sequelae. Lacrimation, swelling lids, itching, foreign body sensation and periorbital pain were common features with bilateral involvement in the majority of cases. Approximately 48% of eyes had a mucopurulent discharge. Preauricular lymphadenopathy, keratitis and subconjunctival hemorrhage were observed in 16.2%, 12.6%, and 10.1% of affected eyes, respectively. Respiratory disturbances accompanied the eye signs in some cases. Only one case developed neurological complications: facial palsy was observed for three months without recovery.

## INTRODUCTION

Over the past two decades, outbreaks of acute hemorrhagic conjunctivitis (AHC) have occurred in many countries all over the world following the first epidemic in West Africa in 1969 and the second in Southeast Asia in 1970 (Chatterjee *et al*, 1971; Lim *et al*, 1971; Parrott 1971; Jones, 1972; Kono *et al*, 1972; Mitsui *et al*, 1972; Yin-Murphy 1972; Wolken, 1974; Yang *et al*, 1975; Whitcher *et al*, 1976; Sklar *et al*, 1983). The causative agents of AHC are two picornaviruses, a new enterovirus type 70 (EV70) isolated from epidemics in Morocco, Singapore, Japan and Thailand in 1971 (Kono *et al*, 1972; Lim *et al*, 1973; Yin-Murphy 1973; Mirkovic *et al*, 1974; Thongcharoen *et al*, 1978) and a new coxsackie virus type A24 variant (CA24v) isolated during 1970 epidemic in Singapore and 1975 elsewhere in Southeast Asia (Lim *et al*, 1971; Yin-Murphy 1972, 1973 a, b; Mirkovic *et al*, 1974; Bahrin *et al*, 1976; Thongcharoen *et al*, 1978; Tan *et al*, 1980). Although the clinical features are indistinguishable, viral conjunctivitis due to EV 70 is highly contagious, spreading worldwide, resulting in a pandemic and more severe illness with hemorrhage than CA24v. Moreover, outbreaks caused by CA24v are more explosive and extensive than EV 70. Furthermore, EV 70 infected cases develop polio-like motor paralysis as a neurological complication which is rare in CA24v infec-

tion (Wadia *et al*, 1972; Kono *et al*, 1974; Green *et al*, 1975).

The purpose of this study is to evaluate the clinical manifestations of an AHC outbreak in Thailand in 1992, the complications and sequelae, including identification of the etiologic agent, in order to help clinicians to recognize the illness and institute appropriate prevention and control.

## MATERIALS AND METHODS

### Study population

During October through December, 1992, 260 patients with 444 affected eyes, who presented to the Outpatient Department (Ophthalmology) at Siriraj Hospital with signs of acute conjunctivitis were prospectively enrolled in the outbreak study. Patients with an obvious allergic, or chemical conjunctivitis were excluded. History taking included the patients' age, address, occupation, history of contact, and ocular symptoms. Slit-lamp biomicroscopic eye examination was performed in all cases.

### Specimen collection

After instillation of topical tetracaine hydrochloride 0.5% in patients' eyes with their permis-

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sion, swabs of the superior and inferior palpebral conjunctiva of affected eyes were taken, immersed in viral transport media and sent to the laboratory for viral culture in 88 cases. Sixty-one throat swabs were also collected at the first visit. One hundred and one blood samples were collected on the same day, but only 42 convalescent serum two weeks later were available. Therefore the 59 unpaired sera were excluded from the study.

### Viral isolation and identification

Three cell lines, HeLa, HEp-2 and human embryonic fibroblasts were used for viral isolation. Each tube of monolayer cell culture was inoculated with 0.2 ml of conjunctival and throat swabs in duplicate. The swab specimens were collected in viral transport media (2% fetal bovine serum in minimal essential media with 100 units/ml penicillin, 100 µg/ml streptomycin and 2 µg/ml fungizone). The inoculated cells were incubated at 35°C and observed daily for cytopathic effects (CPE). The cell culture showing CPE was identified by indirect immunofluorescence technique using rabbit antisera to CA24v (anti EH 24, CDC, USA) and to EV70 (Strain J 670/71, CDC, USA). The positive cells showed an apple green color under fluorescent microscope.

### Serology

Paired sera were collected from patients and were tested for neutralizing antibody to CA24v and EV70 by microneutralization technique. Antibodies to herpes simplex virus and adenovirus were evaluated by using complement fixation test. These techniques were performed as previously described (Schmidt, 1989).

## RESULTS

The patients age ranged from 1 to 83 years old, with a mean  $\pm$  SD of  $30.7 \pm 15.9$  years. More females than males were affected (56.1%). There were 79.2% of cases living in Bangkok, and 20.8% of cases coming from other regions of Thailand. Sixty-nine percent of patients had a history of contact, from family (57.8%), hospital and clinic (17.8%), company and factory (12.4%), school

(3.2%), and others (8.6%). The incubation period varied from less than 24 hours to three days in 68.7% of cases (1-21 days). Unilateral conjunctivitis was first presented in 158 out of 260 cases (60.3%), and then rapidly spread to the other eye. Therefore, bilateral conjunctivitis was found in 70.8%. The onset was sudden with the chief complaints of excessive lacrimation (63.3%), lid swelling (58.6%), itching (58.3%), and foreign body sensation (55.6%), as shown in Table 1.

The common signs of AHC were conjunctival injection (88.5%), preauricular lymphadenopathy (16.2%), cornea lesion (15.3%), subconjunctival hemorrhage (10.1%), (Table 2). Corneal involvement were found in some cases, including focal superficial punctate keratitis (8.1%), diffuse keratitis (4.5%), and subepithelial opacity (2.7%).

Table 1  
Common symptoms in AHC outbreak in Thailand, 1992.

	% Eye finding
Lacrimation	63.3
Swelling lids	58.6
Itching	58.3
Foreign body sensation	55.6
Periorbital pain	50.2
Mucopurulent discharge	48.4
Irritation	39.9
Burning sensation	7.0

NB: More than one symptom in one patient

Table 2  
Common signs in AHC outbreak in Thailand, 1992.

	% Eye finding
Conjunctival injection	88.5
Preauricular lymphadenopathy	16.2
Cornea involvement	15.3
Subconjunctival hemorrhage	10.1

Table 3

Association between coxsackie A 24 variant isolation and neutralization test.

Neutralization test	Isolation					
	Eye swabs			Throat swabs		
	Positive	Negative	Total	Positive	Negative	Total
Four-fold rising antibody	15	6	21	5	6	11
Inconclusive	8	6	14	2	8	10

Ninety-seven out of 260 cases (37.3%) were associated with systemic involvement such as upper respiratory tract infection (63.9%), pharyngitis (21.6%), fever (16.5%), headache (5.1%), and gastrointestinal disturbances (5.1%).

The course of AHC lasted mostly about 5 days (1-30 days) depending on the extent of organ involvement. However, keratitis healed slowly in about 7-10 days. There was one case of this outbreak having neurological complications: facial palsy occurred 1 week after eye involvement, with focal keratitis of both eyes and resolved within one month without neurological recovery in 3 months follow up.

Coxsackie A 24 variant, the etiologic agent, was demonstrated in 73 out of 95 cases (76.8%). From 88 conjunctival swabs, 60 strains of CA24v were isolated (68.2%). Twenty strains of CA24v were recovered from 61 throat swabs (32.8%). A four-fold neutralizing antibody (NA) to CA24v rising from < 10-40 to 40-160 was found in 25 out of 42 patients (59.5%). However, positive results by all techniques were found only in 4 out of 21 cases (19%). The four-fold rising titer of NA was associated with positive eye isolation in 15 out of 21 cases (71.4%) and positive throat swab culture in 5 out of 11 cases (45.5%), as shown in Table 3. A four-fold rise of antibody to adenoviruses and herpes simplex viruses in acute and convalescent sera were not found in the study group.

## DISCUSSION

Viral conjunctivitis is one of the most common contagious ocular diseases. It can occur as small outbreaks or epidemics, or as a pandemic. AHC has become the most prominent enterovirus epidemic

disease in Southeast Asian countries with a wide variety of manifestations (Yin-Murphy *et al*, 1987).

Regarding to our study, the outbreak of AHC in Thailand in 1992 affected all age groups and females predominantly, similar to Yin-Murphy's report (Yin-Murphy *et al*, 1986, 1987). Bilaterality (70.8%) was found to be higher than the 58-70% in other reports (Yin-Murphy *et al*, 1976, 1986, 1987) and slightly less than the 71-88% in some reports (Goh *et al*, 1976; Tan *et al*, 1980). As Table 1 shows, the most common symptom of AHC caused by CA 24v in Thailand is excessive lacrimation (63.3%), contrary to lid swelling in Singapore and Taiwan outbreaks (Goh *et al*, 1976; Yin-Murphy *et al*, 1976, 1986; Bureau, 1986), and periorbital pain (94%) mostly reported in the 1979 Vellore, India epidemic (Christopher *et al*, 1982). In general, the other symptoms found in the Thailand outbreak, 1992 are lid swelling, itching, foreign body sensation, and periorbital pain, as shown in Table 1. However, 48.4% of affected eyes had mucopurulent discharge, compared with 9.7-40% in many reports (Lim *et al*, 1971; Goh *et al*, 1976; Tan *et al*, 1980; Yin-Murphy *et al*, 1987). The secondary bacterial infection is probably due to neglected, poor hygiene status, and delayed management.

From Table 2, preauricular lymphadenopathy (16.2%) is observed less than by other investigators (17.6-51%) (Lim *et al*, 1971; Yin-Murphy *et al*, 1976; Goh *et al*, 1976; Tan *et al* 1980; Bureau, 1986). Superficial epithelial keratitis with few focal areas, and rarely diffuse keratitis (12.6%) found in our study are in the middle range of the 1.5-27% reported in many series which resolve in one to two weeks (Lim *et al*, 1971; Tan *et al* 1980; Yin-Murphy *et al*, 1986, Bureau 1986). However, 2.7% of affected eyes had subepithelial opacity, contrary to no report in association with CA24

AHC (Chen *et al*, 1989). Possible delayed examination may result in this finding. Subconjunctival hemorrhage is found 10% of affected eyes which is less than the 11-43% in some reports (Lim *et al*, 1971; Yin-Murphy *et al*, 1986; Bureau, 1986) although other series report less than 8% and non-hemorrhagic signs as well (Bahrin *et al*, 1976; Yin-Murphy *et al*, 1976, 1987; Tan *et al*, 1980; Christopher *et al*, 1982; Brooks *et al*, 1989). Generally, subconjunctival hemorrhage in AHC can be pinpoint, petechiae, small round spots, or diffuse patches, with early occurrence on the first day in the majority of cases. Moreover, gross hemorrhage is more easily observed than pin points. Furthermore, the complication of iritis is rare, similar to reports by Lim *et al* (1971) and Tan *et al* (1980).

The clinical manifestations of AHC caused by EV 70 epidemic in 1971 in Thailand were more pronounced than this outbreak except for the occurrence of less subconjunctival hemorrhage (8%) and keratitis (12%) (Dumavibhat *et al*, 1973). In general, the effects of CA24v AHC infection subside and resolve quickly within one week, in a short course without sequelae.

Extraocular symptoms and signs (37.3% of total cases) are usually mild and resolve without sequelae. Upper respiratory tract infection associated with CA24v AHC was reported in 23.8% of cases, more frequently than gastrointestinal tract involvement, contrary to other series reports of 3.8-83% of cases (Lim *et al*, 1971; Goh *et al*, 1976; Tan *et al*, 1980; Yin-Murphy *et al*, 1976, 1986).

Although neurological complications such as radiculomyelitis, palatal paresis and facial palsy observed in EV 70 AHC infection had not been reported in CA24 infection (Thakur *et al*, 1981; Wadia *et al*, 1981; Kono, 1985; Chopra *et al*, 1986) one case of this outbreak had facial palsy following AHC for one week. Unfortunately, the causative agent could not be isolated and only a two-fold rising of neutralizing antibody to the CA 24 variant was demonstrated (1 : 20 in first serum to 1 : 40 in convalescent serum collected 2 weeks later) contrary to no case of neurological findings in many series (Lim *et al*, 1971; Goh *et al*, 1976; Tan *et al*, 1980; Yin-Murphy *et al*, 1976, 1986; Christopher *et al*, 1982; Bureau, 1986). Therefore, this case cannot rule out other causes. Neurological complications accompanying or following AHC may be attributed to concurrent infection with other viruses (Green *et al*, 1975; Bureau, 1986).

The CA 24 variant can be isolated from conjunctival swabs, scrapings, tears, throat swabs and garglings, as well as feces (Yin-Murphy, 1989). From our study, 68.2% of 88 conjunctival swabs yielded viral isolates, more than 32.8% of 61 throat swabs, but less than Singapore's isolation rates, which were in 83.6% and 77.7% respectively (Yin-Murphy *et al*, 1986). However, Tan *et al* (1980) reported a positive isolation rate of only 35%. Furthermore, a four-fold rising of neutralizing antibody to CA24v in our study occurred in 59.5%. The diagnosis of four-fold rising of neutralizing antibody between the acute and convalescent sera is more commonly demonstrated when the convalescent serum is collected 3 to 4 weeks after the onset of conjunctivitis than when collected at 10-14 days after onset (Yin-Murphy, 1989). Thus, the presence of low titer, or absence of antibody rising titer has also been reported by other investigators (Chang *et al*, 1977; Tan *et al*, 1980; Christopher *et al*, 1982). The presence of a high neutralizing antibody titer does not last long, despite previous exposure to the virus with repeated epidemics of CA24v AHC.

Since outbreaks of AHC occur from time to time, rapid and early diagnosis of AHC cases would provide an opportunity to implement appropriate measures for prevention and control.

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