Acute Hemorrhagic Conjunctivitis

Etiology, Epidemiology and Clinical Manifestations

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Acute hemorrhagic conjunctivitis (AHC), which was first recognized as a new clinical entity about twenty years ago, has added a new chapter, “Enteroviral Conjunctivitis,” to textbooks of ophthalmology. Its two major etiological agents are enterovirus 70 (EV70) and coxsackievirus A24 variant (CA24v). These two viruses are clearly distinguished either serologically or genetically from each other, although the diseases they cause are clinically indistinguishable and constitute the AHC syndrome.

The disease is very contagious, and its clinical picture is so characteristic that differentiation from other varieties of viral conjunctivitis is possible. Though the prognosis for the affected vision is favorable, on very rare occasions EV70 conjunctivitis is followed by polio-like motor paralysis.

AHC caused by EV70 infection first appeared in West Africa in 1969 and rapidly spread to various parts of the Eastern Hemisphere in succeeding years; the disease further encompassed many parts of the Western Hemisphere in the second pandemic, 1980-1982. Independently, AHC outbreaks due to CA24v were first recognized in 1970 in Singapore and probably on Java Island, and have been localized mainly in Southeast Asia and India until very recently. Today both causative agents spread almost all over the world.

Molecular epidemiological studies of the viral genomes revealed that EV70 and CA24v suddenly emerged as new human pathogenic agents.
during the latter half of the 1960s and have evolved at a constant rate
over the past twenty years. The viruses served as a useful model for
studying the evolutionary changes of a new human pathogenic virus
which happened to appear in our time.
The plan to publish a book on AHC was initiated by Dr. Reisaku
Kono, one of the discoverers of EV70, and carried out by the editors
after his death in 1985. His original idea was to publish a comprehensive
book which would cover all the aspects of AHC, from its historical
background to the latest findings, including epidemiology, clinical
medicine, laboratory diagnosis, and virology. We thought a book like
this would be useful for all readers in various fields who are interested in
obtaining fundamental knowledge of AHC.
The book is published with the collaboration of more than fifty
authors who have contributed clinical, epidemiological or virological
studies on AHC. To our regret, however, three persons who were to

have contributed as authors passed away before the completion of this
book: Dr. Fakhry Assaad, Director of the Infectious Diseases Unit,
WHO; Dr. Nathalie J. Schmidt, Viral and Rickettsial Disease Laboratory,
California Department of Health Services, U. S. A.; and Dr.
Reisaku Kono, Professor of Microbiology, Saitama Medical College.
Dr. Kono, as mentioned above, is the one who initially planned this
book, and he made a great contribution to the progress of AHC
research by initiating virological and epidemiological studies of EV70.
Therefore, it is appropriate, and certainly our wish, that this book
should be dedicated to his memory.
We are most grateful to all who have contributed to this publication.
We also express our thanks to Dr. Akira Nakajima, Professor of
Ophthalmology, Juntendo University School of Medicine, for his kind
advice, and to the Miura Foundation for Medical Research, Japan, for
its financial support of the publication.

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Keizo Ishii
Yukio Uchida
Kikuko Miyamura
Shudo Yamazaki
Introduction

Joseph L. Melnick*

Until recently only a few Coxsackieviruses (type B2) and echoviruses (types 7 and 11) had been isolated from conjunctival swabs. This situation changed markedly when large epidemics of acute hemorrhagic conjunctivitis (AHC) began to break out. The first epidemic occurred in West Africa in 1969 and the second in Southeast Asia in 1970. Credit goes to Yin-Murphy for isolating, during the Singapore epidemic, the first enterovirus incriminated as the causative agent of AHC, an agent that was subsequently identified by a cooperative study of the WHO Virus Reference Centres as a variant of Coxsackievirus type 24 (CA24v). Subsequent outbreaks caused by CA24v have since been identified in Singapore, Hong Kong, and India, but have not spread to other parts of the world.

In the meantime, the AHC outbreak that had initially emerged in Accra rapidly swept along the coastal areas of West, East, and North Africa, reaching India, Southeast Asia, and Japan in 1971. Tens of millions of people were affected during the pandemic. Another novel virus was isolated by Yin-Murphy et al. in Singapore, by Chang et al. in Hong Kong, by Kono et al. in Japan, and by Nejmi et al. in Morocco. Again, through a cooperative program of the WHO Virus Reference Centres in which Dr. Kono’s laboratory played a key role, the agent was identified and classified as a new enterovirus—type 70 (EV70). As mentioned below, EV70 continues to be the agent most often associated with AHC, and we are indebted to the late Reisaku Kono for much of our knowledge of this virus.

The disease, generally localized to the eye, is characterized by subconjunctival hemorrhage. EV70 is highly contagious, spreading rapidly under crowded and unhygienic conditions; warm, humid, coastal climates seem to be particularly favorable for its transmission. Intrafamilial spread is common. Some localized outbreaks, especially in developed countries, have centered around eye clinics.

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antibodies appeared in the populations involved. Multiple epidemics have occurred within a 5-year period in the same regions, particularly in Southeast Asia, suggesting that immunity may be short lived.

Until 1981 virtually no infection or disease caused by EV70 had been reported in Australia and the Americas. Among more than 1,000 serum samples collected between 1971 and 1974 from residents of the United States, only 3 contained antibodies to the virus. Nevertheless, when the virus was introduced into USA in 1980, a secondary spread did not take place. However, in 1981 this situation changed. Early in 1981 AHC reappeared in some of the countries from which it had been absent for a number of years. The disease spread widely in Africa and Asia, and this time it also spread extensively in the Caribbean area, in northern South America, and in Central America during the spring and summer of 1981. In the early autumn an explosive outbreak occurred in Miami, Florida, involving thousands of cases. The diagnosis and study of AHC caused by EV70 have been complicated by the difficulty of isolating the virus. Most of the recent outbreaks have been identified solely by serological means.

EV70 isolates obtained from widely separated locales (Asia and the Americas) during the same pandemic period, 1980-81, were found by Dr. Kono’s laboratory to be closely related by ribonuclease T1-resistant oligonucleotide mapping. However, two isolates obtained from Japan and from Morocco during the first AHC pandemic of 1969-72, although closely related to each other, differed from the 1981 strains by many oligonucleotides. The similarities among contemporaneous strains from distant regions suggest that only one basic genotype of this virus appears to be in circulation worldwide at any one time.

Since epidemics of enteroviral conjunctivitis had never been known before 1971, Dr. Kono had proposed a two-foci theory for the first pandemic of AHC (1969-72), which was based on the assumption that EV70 and CA24v might have been derived from the same origin or might comprise a common enterovirus group. If either assumption is correct, EV70 and CA24v should have partial homology in their nucleotide sequences, although they are serologically distinguishable. Consequently, his laboratory compared representative strains, J670/71 for EV70 and EH24 for CA24v, by serology and RNA homology. The results clearly demonstrated the viruses to be serologically distinct and to lack any homology between their genomes. Recent serologic and RNA homology studies comparing EH24 with other variants of CA24 virus established that this isolate shares RNA homology and serologic cross-reactions with other CA24 viruses, confirming the results of earlier WHO collaborative studies.

As a consequence of these studies, Dr. Kono concluded that AHC started
from a single focus in West Africa, very likely in Ghana, and that the etiologic
agent, EV70, is an enterovirus that has newly appeared and has been undergoing
a continuing evolution at a constant rate in many parts of the world
during recent years. At about the same time, a variant of CA24 evolved independently
in Southeast Asia.
It is apparent from this brief introduction and from the chapters that follow
that Reisaku Kono has been a key figure in the investigations of AHC, and
his contributions will be long remembered.