Acute Hemorrhagic Conjunctivitis

Etiology, Epidemiology and Clinical Manifestations

Editors
T. Uchida, Saitama
K. Ishii, Tokyo
K. Miyamura, Kyoto
S. Yamazaki, Tokyo

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Contents

Preface

Introduction
J.L. Melnick xi

I. EPIDEMIOLOGY

Ocular Enterovirus Infections in the World
Y. Ghendon 3

Acute Hemorrhagic Conjunctivitis in the Eastern Hemisphere
I. Two Pandemics of EV70,1969 to 1972 and 1980 to 1982
K. Ishii 11

Acute Hemorrhagic Conjunctivitis in the Eastern Hemisphere
II. AHC Epidemics and Sporadic Cases of AHC in Non-Epidemic Periods
K. Ishii 35

Acute Hemorrhagic Conjunctivitis in the Western Hemisphere (1980-87)
J.C. Hierholzer and M.A. Pallansch 49

Epidemics of Acute Hemorrhagic Conjunctivitis by Coxsackievirus A24 Variant
M. Yin-Murphy 57

Seroepidemiology of Enterovirus 70 and Coxsackievirus A24 Variant
K. Miyamura 67

Acute Hemorrhagic Conjunctivitis in Areas

Epidemiology in Ghana
J.A.A. Mingle 89

Epidemiological and Clinical Studies of Two Outbreaks of AHC in 1970-71 and 1984-85 in Morocco
S. Nejmi and O.G. Gaudin 95

Acute Hemorrhagic Conjunctivitis in Tunisia
B. Nabli 105

Acute Hemorrhagic Conjunctivitis in South Africa
H.G.V. Küstner 111

Epidemiology of Enteroviral Conjunctivitis in Europe
R. Sohier and J.-J. Chomel 117

Epidemics of Acute Hemorrhagic Conjunctivitis in Pakistan
A. Ghafoor and M.I. Burney 123

Epidemiology of Acute Enteroviral Conjunctivitis in India
T.J. John and G. Sridharan 129
Acute Hemorrhagic Conjunctivitis in Malaysia (1970-85)

...............................D.S.K. Tan and M. Yin-Murphy 135

V

vi CONTENTS

Acute Hemorrhagic Conjunctivitis in Thailand
P. Thongcharoen and C. Wasi 139

Epidemiological and Etiological Studies of Acute Hemorrhagic Conjunctivitis in China
Fang-Chou Ku 151

Acute Hemorrhagic Conjunctivitis in Hong Kong
Wai-Kwan Chang 157

Acute Hemorrhagic Conjunctivitis due to Enterovirus 70 in China (Taiwan)
Chen-Wu Chen 161

Acute Hemorrhagic Conjunctivitis in Korea
S.W. Rhee 167

Epidemiology of Acute Hemorrhagic Conjunctivitis in Japan, Including a Study in Mie Prefecture
N. Sakurai, K. Miyamura, and K. Ishii 171

Epidemiological Surveillance of Acute Hemorrhagic Conjunctivitis in Japan, 1981-86
K. Miyamura 185

Epidemic and Epidemiological Survey in Panama
W.C. Reeves, S.L. de Lao, and M.M. Brenes 195

Acute Hemorrhagic Conjunctivitis in Brazil
I. AHC Caused by EV70 in Brazil
A.C. Linhares, E.C.O. Santos, R.B. Freitas, and C.M. Nakauchi 201

II. AHC Caused by CA24v in North Brazil-1987
E.C.O. Santos and A.C. Linhares 209

II. CLINICAL MANIFESTATIONS

Clinical Features of Acute Hemorrhagic Conjunctivitis due to Enterovirus 70
Y. Uchida 213

Clinical Features of CA 24v Acute Hemorrhagic Conjunctivitis
C.-W. Chen, W.-L. Huang, and Y.-F. Hsie 225

Central Nervous System Complications of Enterovirus Type 70 Infection:
Epidemiological and Clinical Features
T.-p. Hung 235

Neurological Manifestations of Enterovirus 70: A 15-Year Review from India
N.H. Wadia 251

Clinical Experience in Geographical Areas

Acute Hemorrhagic Conjunctivities: Clinical Experiences in Ghana
C.O. Quarcoo 269

Acute Hemorrhagic Conjunctivitis in Senegal
J.S. Diallo 273

CONTENTS vii

Enterovirus 70 and Acute Hemorrhagic Conjunctivitis in Tunisia
R. Mabrouk 277

Clinical Experiences with Acute Hemorrhagic Conjunctivitis in the United States
P.A. Patriarca 285

III. LABORATORY DIAGNOSIS

Laboratory Diagnosis of Enterovirus 70

Virus Isolation of Enterovirus 70
N. Nakazuno and K. Kondo 295

Immunofluorescense Diagnosis of Enterovirus 70 Infection
J.L. Melnick and S.R. Pal 307

Laboratory Diagnosis of Enterovirus 70 with Monoclonal Antibodies
M.H. Hatch 311

Serological Diagnosis of Enterovirus 70 Infections
K. Ishii and K. Hikiji 321

Laboratory Diagnosis of Coxsackievirus A24 Variant

Diagnosis of Coxsackievirus A24 Variant
M. Yin-Murphy 337

IV. VIROLOGY

General Characteristics of Enterovirus 70
S. Yamazaki and K. Miyamura 345
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.

* Department of Virology and Epidemiology, Baylor College of Medicine, Houston, Texas 77030, U.S.A.
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

INTRODUCTION xiii
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.