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Short communications

An epidemic of hand, foot, and mouth disease caused by coxsackievirus A6 in Osaka City, Japan, in 2017

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Summary:

The second largest epidemic of hand, foot, and mouth disease since 1982 occurred in 2017, which involved 6,173 cases in Osaka City, Japan. The main causative agent was coxsackievirus A6 (CV-A6). Phylogenetic analysis revealed that the detected CV-A6 strains belonged to genetic group A3 and A4 in clade A.

Text:

Hand, foot, and mouth disease (HFMD) is a common childhood disease caused by human enteroviruses (EVs) belonging to the genus Enterovirus, family Picornaviridae (1). EV-A71 and coxsackievirus (CV)-A16 have been recognized as the main causative agents of HFMD for many years (1). After the emergence of CV-A6 as the main causative agent of HFMD in Osaka City, Japan in 2011, CV-A6 has subsequently caused large HFMD epidemics every 2 years (2).

Among the structural proteins of EVs, viral protein 1 (VP1) is exposed on a virion's surface, and it has been considered to contain neutralization epitopes (3; 4). A phylogenetic tree based on complete VP1 sequences classified CV-A6 strains into seven distinct genetic clades (A–G): clade A was sub-classified into four distinct genetic groups (A1–A4) (2; 5). All CV-A6 strains detected in Osaka City between 2011 and 2015 were...
classified as clade A (2). Genetic group A1 was detected in 2011, whereas genetic group 
A3 was mainly detected in 2013 and 2015 (2). Additionally, changes in viral diversity 
have coincided with CV-A6 outbreaks reported worldwide, including the 2008 Finland 
outbreak and major outbreaks affecting Asia, Europe, and the United States in 
subsequent years (6). Although the relationship between genetic diversity and 
epidemics has been reported previously, the underlying mechanisms of the evolution 
and emergence of novel genetic groups remain unclear because analyses of antigenicity 
and molecular epidemiology remain insufficient worldwide.

Totally, 6,173 cases of HFMD were reported from approximately 60 pediatric 
 sentinel sites in Osaka City in 2017, marking the second largest HFMD epidemic since 
the introduction of the National Epidemiological Surveillance of Infectious Diseases in 
1982 in Osaka City (Figure 1A). Among patients with HFMD in 2017, 48.2% 
(2973/6173), 80.6% (4974/6173), and 93.0% (5738/6173) were <2, <4, and <6 years old, 
respectively. Surveillance was conducted in 2017, wherein 13 throat-swab, 12 feces, 2 
nasal mucus, 1 airway mucus, and 1 cerebrospinal fluid samples were collected from 29 
patients with HFMD. In total, 62.1% (18/29) of patients were <2 years old, potentially 
indicating a susceptible population for EV infection. EV genomes were screened using 
real-time reverse transcriptase-polymerase chain reaction (RT-PCR) (7). EV-positive
specimens were further analyzed via semi-nested RT-PCR targeting VP1 (8). The complete VP1 sequences were determined for CV-A6-positive specimens (2). Of the 29 specimens, 24 (82.8%) were positive for EVs, including 18 (62.1%) for CV-A6 (10 throat-swab, 7 feces, and 1 airway mucus), 4 (13.8%) for EV-A71 (3 feces, and 1 throat-swab), 1 (3.5%) for echovirus (Echo) type 3 (1 feces), and 1 (3.5%) for Echo type 7 (1 feces). Among 18 CV-A6-positive specimens, 17 complete VP1 sequences were identified in 2017: and deposited in GenBank under the accession numbers LC419996–LC420012. All 17 CV-A6 strains were classified as clade A (Figure 1B). These strains were further divided into genetic group A3 (64.7%, 11/17) and A4 (35.3%, 6/17). The complete VP1 sequences of genetic group A3 in 2017 exhibited 94.6%–99.3% and 98.3%–100% nucleotide and amino acid identity to genetic group A3 strains detected in Osaka City in 2013 and 2015, respectively. Additionally, the upsurge of genetic group A4, which differs from the conventional genetic groups, was confirmed in 2017 since its initial detection in 2009 in Japan and reemergence in 2015 in Osaka City. Genetic group A4 was one of the major epidemic strains in 2017. Comparison of the complete VP1 sequences of CV-A6 strains detected in 2017 and the strains detected in 2009 and 2015 revealed 93.2%–96.0% and 98.0%–98.7% nucleotide and amino acid identity, respectively. All CV-A6 strains classified into genetic group A4 in Osaka City in 2017
possess a Ser137Asn amino acid substitution, which is located in a region presumed to be especially highly exposed in the complete amino acid sequences of VP1, compared with genetic group A3 strains in Osaka City in 2013 and 2015.

We clarified that CV-A6 was responsible for HFMD epidemics in Osaka City every two years since 2011, when CV-A6 appeared as the main causative agent of HFMD in Osaka City, until 2017. The epidemiology of Japan revealed a similar trend (9). We considered that population immunity and antigenic differences may be important factors in the recent HFMD epidemics caused by CV-A6 because strains with amino acid mutations in antibody-accessible regions on the surface of VP1 or with different genetic backgrounds certainly emerged and caused large epidemics. The emergence and predominance of CV-A6 strains with different genetic backgrounds and amino acid mutations may be induced by immunological pressure in an effort to escape host immunity. Continuous monitoring of CV-A6 activity and antigenicity analysis will elucidate these issues. Additionally, genetic group A4 has been responsible for large-scale HFMD outbreaks since 2013 in China (10). Thus, this genetic group may be spreading across Asia. The accumulation of knowledge about this emerging pathogen may provide insights to the prevention and control of HFMD as well as in vaccine development.
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Conflict of Interest:

The authors declare that they have no conflict of interest.

Ethical statement:

This work was approved by the ethics committee of the Osaka Institute of Public Health (No. 1709-08).
References


Figure Legend

Figure 1A. Yearly distribution of HFMD in Osaka City, Japan from 1982 to 2017. HFMD patients were identified in accordance with the diagnostic criteria of the Ministry of Health, Labour and Welfare of Japan, which include a vesicular rash on the hands, feet, and oral mucosa. Clinically diagnosed HFMD patients are weekly reported to the Infectious Disease Surveillance Center from the pediatric sentinel sites in Osaka City since 1982.

Figure 1B. Maximum likelihood phylogram based on complete coxsackievirus A6 (CV-A6) viral protein 1 nucleotide sequences (915 nucleotides). A phylogenetic tree was constructed using 69 strains, including 42 that were detected in Osaka City between 2011 and 2017 and 27 reference strains retrieved from GenBank, using MEGA version 7.0 (http://www.megasoftware.net) and the Tamura-Nei model. Initial trees for the heuristic search were obtained automatically by applying the neighbor-joining and BioNJ algorithms to a matrix of pairwise distances estimated using the maximum composite likelihood approach and then selecting the topology with the superior log likelihood value. The numbers at the nodes indicate the bootstrap support values, expressed as a percentage of 1000 replicates (values smaller than 75 were omitted). The scale bar indicates genetic distances. Black and white circles indicate the CV-A6 strain
detected in Osaka City in 2017 and the CV-A6 strains detected in Osaka City from 2011 to 2015, respectively. White squares indicate the CV-A6 strains detected in the rest of Japan. Each strain ID consists of a three-letter abbreviation of the country and the year of detection. The accession number is provided at the end of the strain ID in parentheses.

ESP, Spain; FIN, Finland; FRA, France; JPN, Japan; CHN, China; TWN, Taiwan; USA, United States of America.
Figure 1A (Kanbayashi et al.)

Number of reported HFMD cases

Year


2024 1189 1336 2927 2090 516 892 618 1119 266 827 2581 2623 452 1372 1615 718 489 2087 4210 4211 6391 6173