Update on Enterovirus 71 Infections: Epidemiology, Molecular Epidemiology, and Vaccine Development

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Abstract

Enterovirus 71 (EV71) infections are one of the main etiological agents of hand, foot and mouth disease (HFMD), or herpangina, worldwide. The purpose of this study was to explore the epidemiology and molecular epidemiology of EV71 infection as well as the prospects for the development of an EV71 vaccine. We performed a search for “enterovirus 71” and “epidemiology” or “molecular epidemiology” or “vaccine” in Medline and PubMed to search through previous studies. Only articles that were published in the English language were included for review in this study. The morbidity of EV71 infection was different among different countries; seasonal variations in its incidence were also observed. Most patients with EV71 infection were children below 5 years of age. The organ most likely involved in EV71 infection is the brainstem. The infection’s genetic lineages are undergoing rapid evolutionary changes. The association between the occurrence of EV71 infection and the circulation of different genetic strains of EV71 virus (genotypes B3, B4, C1, C2, C4, and C4a) has been identified around the world. EV71 infection is an important life-threatening communicable disease, and there is an urgent global need for vaccine development for the prevention and control of EV71 epidemics. To establish a global surveillance system of EV71 infection for the identification and detection of the potential emergence of new EV71 variants is needed in the future.

Keywords: Epidemiology; Herpangina; Enterovirus 71; Vaccine

Introduction

There are four species of human enteroviruses: human enterovirus A (HEV-A), HEV-B, HEV-C, and HEV-D. The classification of human enteroviruses is based on each strain’s homology within the RNA region coding for the VP1 capsid protein [1]. Enterovirus 71 (EV71) is classified into the human enterovirus A (HEV-A) species of the Picornaviridae family [1].

Enterovirus 71 is one of the important causative agents of hand, foot, mouth disease (HFMD) and herpangina [1-3]. The clinical spectrum of EV71 infection is wide. It includes skin eruptions, internal organ, and neurological manifestations, and even death. In recent years, there are several large-scale epidemics of EV71 infection with severe neurological complications involving the central nervous system (CNS) in children reported. Although the EV71 virus is isolated in many countries, epidemics of the EV71 infection have been predominantly found in the Asia-Pacific region [2-8]. However, the reasons for this phenomenon are uncertain. For the reason of the potential of the virus to cause severe neurologic disorder and death, we need to know the features of and control measures for EV71 infection. The purpose of this study was to explore the epidemiology and molecular epidemiology of EV71 as well as the prospects for the development of an EV71 vaccine.

Data sources

All papers published between January 1965 and August 2017 related to EV71 infection were extracted by searching Medline (National Library of Medicine, Bethesda, Maryland, USA) and PubMed using the phrase “enterovirus 71” and “epidemiology” or “molecular epidemiology” or “vaccine.” The results were limited to articles available in English. Additional citations were identified from the references of relevant literature. Data collection was performed in April and May of 2018.

Epidemiology

In 1969, EV71 was first isolated from a child with encephalitis in US [1]. Several EV71 epidemics were then reported in the 1970s by various countries in the Americas, Europe, Australia, and Asia [2,4-7,38].

In the Asia-Pacific region, a large EV71 epidemic occurred in Sarawak, Malaysia in 1997 [12]. During the same period, there was an EV71 outbreak with four fatal cases reported in Malaysia [12], and a handful of cases with severe neurological disorder were reported in Japan [7]. In 1998, a huge outbreak of EV71 infection occurred in Taiwan [2]. In this outbreak, 405 hospitalized children with serious neurological complications, and 78 died were reported. In 2008, a large-scale outbreak occurred in China, in which approximately 490,000 children with EV71 infections and 126 deaths were reported [8]. In addition to these epidemics, a pattern of 2- to 3-year cyclic epidemics has been observed in various countries or regions, including Japan [13], Sarawak [4,16], and Taiwan [2].
Outside of the Asia-Pacific region, small outbreaks or sporadic cases have occurred in North America, Europe, and Africa in recent decades [25-35]. A low level of the EV71 virus circulates in these regions [25-35]. In 1975, there was a large EV71 outbreak in Bulgaria, in which 140 cases were complicated with paralysis and 27 cases died [27]. In 1978, there was an outbreak of EV71 infection in Hungary, in which the main clinical spectrum was meningitis and encephalitis [34]. In 1998, 20 children experienced severe EV71 infections in Canada [28]; among these cases, 50% of them involved neurological organ with aseptic meningitis, and one-third had clinical manifestations of respiratory tract. However, most of the cases recovered rapidly. In the USA, several small outbreaks of EV71 infection with neurological involvement occurred in 2003 and 2005 [29]. Among these outbreaks, 16 children aged younger than 9 years old were affected, and one child died. One study in Austria found that 9% of children who were infected with EV71 were hospitalized with aseptic meningitis between 2001 and 2004 [20]. In the year of 1998 and 2006, a number of 32 severe cases of EV71 infection with neurological involvement or clinical symptoms related to EV71 infection including cutaneous, visceral, or neurological manifestations was identified in the UK [31]. In 2007, after 21 years of a low level of endemicity, there were 58 patients of EV71 infection with CNS involvement reported in the Netherlands [32]. Widespread circulation of EV71 was reported in Norway between 2002 and 2003 [33]. In this outbreak, EV71 virus was isolated from 19 (17%) of 113 healthy children. In addition, between 1999 and 2000, there were two outbreaks of EV71 infection occurred in HIV treatment centers in Nairobi, Kenya [34].

Seasonal epidemic patterns of EV71 infection were observed in some countries. In Asia, a higher incidence was observed during the summer months [35,39,40]. Some studies have showed a variation in the peak season between different years [13,41]. Most cases of EV71 infection occurred in children five years of age and younger, and males had a higher risk of EV71 infection than females [4].

It is postulated that the reasons for the seasonal patterns of EV71 infection are due to host immune competencies related to fluctuation changes which influenced by seasonal factors. These could include the levels of melanin or vitamin D; seasonal variation, behavioral risk factors (e.g., school attendance, indoor crowding), or environmental factors (e.g., meteorological factors) [1,17,34,36]; however, human behavioral risk factors alone cannot explain the reason of seasonal variation observed for certain cases of EV71 infection, for example, cases that occur in school-aged children or in association with household crowding [35]. The relationship between climatic factors and the occurrence of EV71 infection has been studied. The previous study [36] conducted in Taiwan showed that the higher incidence rate of EV71 infection was significantly related to summer season (from April to June); the occurrence of EV71 infections started to increase once the temperature rose above 13°C; above a temperature of approximately 26°C, the number of cases started to decrease, producing an inverted V-shaped relationship. This study demonstrated that higher temperatures and humidity lead to an increasing the number of EV71 infection in Taiwan.

Clinical characteristics of EV71 infection

Most EV71 infections result in mild clinical symptoms, including herpangina and hand, foot and mouth disease (HFMD). However, some patients progress to severe or fatal illness [1]. Viremia occurred more frequently in children aged one year or younger [41,42]. Most of patients with viremia did not reflect a significant manifestation on the clinical severity of EV71 infection. In addition, the occurrence of patients with CNS involvement was not different statistically between patients with or without viremia [42,43].

EV71 is a highly neurotropic virus [44]. The most common organ of EV71 involvement is brain stem [44,45]. It has hypothesized that there are two likely routes by which the EV71 virus involves the CNS: the EV71 virus is either transmitted to the CNS from the blood across the blood-brain barrier (BBB) or enters the CNS through peripheral nerves via retrograde axonal transport [46,47].

According to the data in mice study, the strong neurotropism of EV71 and retrograde axonal transport in neurons might represent the major transmission route of EV71 [46,48]. In previous studies [46-49], that mice were infected via the oral and parenteral routes with a murine-adapted virus strain that originated from a fatal human case, and the results showed that the EV71 virus entered the CNS via peripheral motor nerves after a skeletal muscle infection and spread within the CNS through motor and other neural pathways. Inflammation was found to be the most marked in the spinal cord gray matter, brainstem, hypothalamus, and subhalamic and dentate nuclei in an autopsy sample in Malaysia [49]. Previous studies [50,51] found that the EV71 infection process was primarily in the respiratory tract epithelium and then able to enter a pre-conventional dendritic cell population of dendritic cells at the infection site; these cells could potentially transmit the virus from local sites to other organs through blood stream during the infection process.

EV71 infection can lead to severe or fatal disease due to pulmonary edema. It is unclear the mechanism of pulmonary edema among severe case with EV71 infection. The previous evidences [52,53] indicate that brainstem involvement of EV71 infection is an important etiology of neurogenic pulmonary edema. The combination of the interactive effect of the virus and the host is vital for viral replication, virulence, and pathogenicity during the viral life cycle [54]. However, tissue-specific viral virulence remains unclear in both cell-based systems and animal models. It needs further study in the future.

Molecular epidemiology

Using the VP1 protein for analysis, EV71 can be divided into four distinct genotypes (A, B, C, and D) [37]. Genogroup A comprises the prototype EV71 strain (BcCr-CA-70) was first isolated in 1969 in the United States [40], but not identified until 2008 [8]. Genotype B can be divided into genotypes B1-B5 and genotype C can be divided into C1-C4 furtherly [17]. Genotype D was identified in India, and genotypes E and F were identified in Africa [28,39].

The phylogenetic origins of the EV71 strains recently circulating in the Asia-Pacific region are showed in Table 1 [2-18,38]. Genotype A is not identified in Asia-Pacific region until 2008 [8]. In contrast, genogroup B and C viruses have been leading to several large-scale outbreaks in Asian region since 1997 [18]. The four distinct genogroups (B3, B4, C1, and C2) have been found to co-circulate in the Asia-Pacific region from 1990-2016 (Table 1). Genotype C4, particularly C4a, has emerged in the Asia-Pacific region [39,40,55-71]. The evolutionary branch C4a has crucial nucleotide and amino acid of mutations relative to branch C4b, and these changes may be the reasons for the increasing of its neurovirulence and risk of outbreaks of EV71 infection in China [61,63,66]. Through genetic and antigenic analysis, genotype C4a viruses of EV71 has been confirmed to spread from China to Vietnam and caused a large-scale epidemic in Ho Chi Minh City and southern Vietnam in 2011 [71].
### Table 1: A summary of human enterovirus 71 genotypes circulating in different countries worldwide, 1960-2016 [2-57].

The phylogenetic origins of the EV71 strains circulating outside the Asia-Pacific region are also presented in Table 1 [19-30]. From 1963 to 1986, EV71 infections were caused by genotypes B0, B1 and B2 in outside the Asia-Pacific region. In contrast, after 1987, the genotype B strain was replaced by genotype C strains of lineages C1 and C2 [19-30]. According to the epidemiological study, the EV71 subgenotypes B1, B2, C1 and C2 appeared to have a global spread.

### Vaccine development

It is believed that close person-to-person contact is the most common route of transmission of EV71 virus. However, the persistent presence of EV71 circulation in the community and the majority of EV71 infections are mild or asymptomatic. These factors result in the lower efficacy of public health interventions, such as hand washing. In the absence of effective treatment, to develop an effective vaccine is the best way to prevent and eliminate EV71 infection. Several EV71 vaccines have been studied, including an inactivated virus vaccine [72-74], a virus-like particle vaccine [75], DNA vaccines [76], a subunit vaccine [77], and a live attenuated vaccine [78-80]. All these vaccines are still in the initial stages of development. Stability, purity, and cost of production are the future challenges of these vaccines.

Due to their stability, the research and development of inactivated EV71 vaccines have progressed further than other types of vaccines. Some studies in China show that Phase III clinical trials of inactivated EV71 vaccines have been conducted [81,82]. These studies involved more than 30,000 infants and children and showed that the safety of the EV71 vaccine is satisfactory in infants and children and that the vaccine can prevent over 90% of EV71-associated HFMD and 80% of EV71-associated disease [72,73,82]. The cost-effectiveness of a national enterovirus 71 vaccination has been done in China [83,84]. They showed the vaccination would be cost-saving or cost-effective to...
prevent EV71 related morbidity, mortality, and use of health service among children aged five or younger, compared to no vaccination. This bodes well for the introduction of a safe and effective EV71 vaccine in the near future. In December 2015, the Food and Drug Administration (FDA) of China approved the first EV71 vaccine [83]. Similar vaccines are being investigated in Taiwan [85] and Singapore [86], both of which have entered Phase I clinical trials. In China, inactivated EV71 vaccines are currently in commercial production.

It still has big challenge of inactivated EV71 vaccine. Although both C4-based and B4-based antibodies cross-neutralized the current circulating EV71 isolates [87], the B4 vaccine poorly neutralized an atypical C2 strain [88]. In addition, no formalin-inactivated EV71 vaccines protected against CAV16, which is primary cause of annual HFMD outbreaks, and humoral immunity correlated with protection but waned after the first 6 months of vaccination [73,87]. However, inactivated EV71 vaccines have an advantage over live attenuated vaccines for safety reasons because of their inability to replicate.

Conclusions

EV71 has been an important etiological agent of infection and death in children in the world. It causes severe neurological symptoms in younger children who become infected. In the absence of effective treatment, to develop effective vaccines is a priority for the prevention and control of EV71 infection. Although inactivated EV71 vaccines have been developed in the last few years, the vaccines have some limitations. At this time, inactivated EV71 vaccines can protect against EV71 but not CAV16 infection. In addition, due to the diversity of enterovirus strains, a sustainable EV71 infection surveillance system should be established in order to identify and detect the potential emergence of new EV71 variants.

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Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals or that were performed by any of the authors.

References


