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Current Status of Research on Coxsackievirus A6 Hand, Foot and Mouth Disease

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Abstract: *HFMD is an acute contagious disease in children caused by enteroviruses. In recent years, the CV-A6 pathogen has become one of the dominant pathogens causing HFMD. However, our knowledge of this new pathogen's epidemiological and genetic characteristics still needs to be improved. In this paper, we review the epidemiological characteristics and genetic recombination of CV-A6, as well as the epidemiological status, epidemiological characteristics, and preventive and control measures of CV-A6 HFMD, to systematically describe the information related to CV-A6 HFMD, and to provide a scientific basis for the subsequent related research.*

Keywords: *Coxsackie virus A6; Hand, foot and mouth disease; Epidemic characteristic*

1. Introduction

Hand, foot, and mouth disease (HFMD) is a prevalent acute contagious disease of the gastrointestinal tract, with a predominant incidence in children under five years of age[1]. The incidence of HFMD is perennially the highest among childhood infectious diseases, and HFMD is the leading cause of death among all statutorily reported contagious diseases in children under five years of age[2]. It causes a significant burden on the health of affected children and has been one of the critical public health concerns. Pathogenic enteroviruses include Coxsackie virus type A (2-8,10,12,14,16), Coxsackie virus type B (2,5), and Enterovirus (EV) 71[3]. Among the major pathogens that cause HFMD include type A human enteroviruses such as EV71, CV-A16, CV-A6, and CV-A10[4]. CV-A6 viruses were first found to be associated with HFMD in an outbreak in Finland in 2008, and CV-A6 is capable of causing not only children but also a more severe form of atypical HFMD in adults. Since 2008, CV-A6 has been the primary pathogen responsible for the occurrence of HFMD epidemics among the adolescent population[5]. Moreover, since 2009, CV-A6 infections have gradually replaced CV-A16 and EV71 infections as the leading cause of HFMD outbreaks in the Asian region[6]. However, our understanding of this new pathogen's epidemiological features and genetic characteristics still needs to be improved. Therefore, this paper will review the epidemiological situation of CV-A6 HFMD and its pathogenetic variation, aiming to provide systematic information for further research on CV-A6 HFMD.

2. CV-A6 Pathogenesis

2.1. CV-A6 Gene Structure

CV-A6 belongs to the small RNA virus family of the genus Enterovirus and is a small, envelope-less, icosahedral virus with a single-stranded positive-stranded RNA genome[7]. The structure of the CV-A6 virion was similar to that of other virions that cause HFMD (CV-A10, EV71, CV-A16)[8].CV-A6 has approximately 7400 nucleotides encapsidated in a highly structured, icosahedral capsid[9], including a 5 '-untranslated area, a 3' -untranslated area, and a single open Reading frame (ORF). The 5 'untranslated region is involved in viral protein translation and RNA replication, and the 3' untranslated region is associated with viral infectivity[10]. The ORF encodes a sizeable multimeric protein cleaved into P1 structural proteins and P2 and P3 non-structural proteins. The P1 structural proteins are processed by viral proteases into the VP1, VP2, VP3, and VP4 coat proteins, with the VP1 subunit forming a pentamer

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around the quintuple axis and the VP2 and VP3 forming a heterohexamer around the triple axis of symmetry of the coat. These structural proteins form the icosahedral capsid of the virus by self-assembly. Among them, the VP1, VP2, and VP3 proteins are located on the exterior of the viral capsid, while VP4 is present on the interior and is a 69-residue-long peptide attached to the inner surface of the capsid. The P2 and P3 non-structural proteins, consisting of 2A-2C and 3A-3D[11], play essential roles in pathogen-host interactions and are closely associated with the host immune response[12].

2.2. CV-A6 Virus Genotyping

Identifying new types within species mainly depends on the similarity of nucleotide and amino acid sequences in the VP1 region[9]. The current genotyping of CV-A6 mainly refers to the genetic distance rule used for EV71 typing[13].CV-A6 can be categorized into four genotypes, A-D, with the B and C genotypes comprising the B1, B2, C1, and C2 genotypes, respectively, and the D genotype comprising the D1, D2, and D3 genotypes, which can be categorized into two branches, D3a and D3b, with D3 genotypes dominating the genotypes in China[12]. The D3 genotype can be categorized into two branches, D3a and D3b. China is mainly dominated by the D3 genotype[14], of which the primary dominant strain causing HFMD epidemics in China is the D3a genotype branch[15]. This typing approach has played a seminal role in the molecular epidemiological characterization and study of CV-A6 in China.

2.3. Genetic Recombination

Recombination is common in EVs and a critical evolutionary strategy for generating genetic diversity. Recombination in unstructured regions rarely affects viral fitness and leads to genetic diversity in viral populations[16]. The variability in different genomic regions suggests multiple recombination events between structural gene regions and the rest of the genome. This phenomenon is consistent with the enterovirus modular evolution model; in this model, the shell gene diversity decides the serological characteristics[17]. D3 Spectrum-A of the CV-A6 subtype proved to be the globally dominant type, with spectrum-A comprising the majority of CV-A6 strains, which has undergone three combinatorial events in terms of large-scale, long-term spread of CV-A6 since 2005, giving rise to an episodic spectrum (spectrum K2) and two endemic spectra (spectrum -J and spectrum-L). Lineage-J included strains isolated mainly from eastern China, and lineage-L may have originated in central and southwestern China and spread northward, eventually spreading throughout the country. This finding suggests that the new recombination may be highly contagious[18]. Gaunt et al., in a study targeting atypical HFMD found in clinics in Edinburgh, UK, found that RF-H had a phylogenetically different sequence of the 3Dpol region. This variation may have been acquired by recombination with serotype A of other human enterovirus species[19]. Whole-genome sequencing of the virus was performed on CV-A6 strains before and during the outbreak, and sequence comparisons revealed significant sequence differences between the strains collected during the outbreak and all previously published non-recombinant CV-A6 strains in the non-coat protein region. It was found that the recombination of this novel CV-A6 virus occurred in the 2C region and that the 2C gene was probably derived from the Coxsackie A4 strain, which is prevalent in the population[20]. This shows that genetic recombination occurs not only between different genotypes of CV-A6 but also between CV-A6 and other enteroviruses. This phenomenon creates conditions for the co-circulation of multiple subgenotypes and the emergence of novel recombinant variants.

3. Trends in the Prevalence of CV-A6 HFMD

3.1. Trends at Home and Abroad

In March of 2008, China's Anhui province had HFMD outbreaks[21]. In May of the same year, HFMD was officially included in managing China's category C legally reported diseases[22]. In the last decade, frequent outbreaks of CV-A6 HFMD have begun to occur globally. The prevalence of CV-A6 has continued to rise year after year, leading to the worst autumn epidemic wave in Guangdong Province, China, since 2008. At the beginning of 2017, the primary pathogens of HFMD in Guangdong were still EV71 and CV-A16.In August and September, CV-A6 infections accounted for 85.5% and 94.8% of all positive HFMD cases. This suggests that CV-A6 dominated the outbreak[23]. A study in the Philippines found that CV-A6 emerged as the significant enterovirus serotype causing HFMD during 2012-2017, with a dominant genotype of D3b/RF-A. Among all HFMD cases that tested positive for enteroviruses, the detection rate of CV-A6 increased from 61.9% in 2012 to 88.1% in 2017, suggesting that the prevalence of CV-A6 is increasing yearly. Most patients were children, with a median age of onset of 2

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years[24]. This shift in dominant pathogens has brought new challenges to preventing and controlling HFMD outbreaks.

3.2. Trends in Genotype Prevalence

The first report of an outbreak of HFMD caused by CV-A6 in China occurred in Guangdong Province[25]. Genotype A and genotypes B and C of the four genotypes of CV-A6 consisted of the prototype strain and some disseminated isolates, respectively. In 1996, 2000, and 2003, genotype D evolved into subtypes D1, D2, and D3, respectively. Subtypes D1 and D2 form a branch with the disseminated strains, suggesting that they are more closely evolutionarily related and less transmissible[18]. It was found that the D2 genotype was predominantly prevalent until 2009, the D2 genotype gradually transitioned to the D3 genotype from 2009-2012, and the D3 genotype became the dominant genotype of CV-A6 from 2013 to the present[26]. Among genotype D, the D3 gene subtype is the leading cause of CV-A6 HFMD outbreaks in China[18], with greater transmissibility, infectiousness, and virulence[25]. The D3a subtype is the dominant causative agent of CV-A6 HFMD in China, with epidemics occurring in Beijing[27], Anhui[28], Tianjin[29], Yunnan[30], Qingdao[31], and other places.

A study of CV-A6 transmission from 2008 to 2015 found that subgenotype D3 was first prevalent within China in 2008 and has been the predominant subgenotype since 2009 before peaking in 2013[25]. Subgenotype D3 is also the primary predominant organism in international epidemics of CV-A6 viruses, such as the D3/Y strain prevalent in Thailand[32].In 2018, the CV-A6 virus detected in the Brazilian HFMD outbreak also belonged to the D3 sub-spectrum[33]. The switch from the D1 and D2 subgenotypes to the D3 subgenotype of CV-A6 viruses reported in Japan around 2009 was completed. By 2010, the D3 genotype had spread throughout Japan, when the D1 and D2 subgenotypes disappeared[34]. During 2019-2022, the D3 subgenome was associated with HFMD epidemics within Thailand, with all CV-A6/TH strains collected belonging to subgenotype D3, with the majority of strains belonging to subgenotype D3.1, and smaller numbers belonging to subtypes D3.2 and D3.5[16]. The future evolution and variation of CV-A6 genotypes and genotypic subtypes have yet to be discovered, and long-term comprehensive monitoring is still required.

4. Epidemiological Characteristics of CV-A6 HFMD

In terms of regional distribution, from 2000 onwards, the center of the global epidemic of HFMD has been the Asia-Pacific region. There is a clustered distribution throughout the country. In China, the hotspot districts of HFMD are mainly concentrated in the southern and eastern areas of China[35]. The highest incidence of HFMD is in the coastal provinces (Hainan, Guangxi, Guangdong), followed by the eastern seaboard (Zhejiang, Shanghai, Jiangsu, Fujian). The inland province of Hunan has also had a high incidence for many years[36].

In terms of population distribution, the majority of HFMD cases are in children under 5 years of age, with a median age of 2.4 years. Among them, children aged 1-2 years were the leading group in terms of severe morbidity and mortality. The proportion of males infected with HFMD was higher than that of females, and this feature is more prominent in severe and fatal cases[37].CV-A6 can cause widespread infection in children, adolescents, and adults, where the onset of the disease can present atypical symptoms[38]. Examples include onychomycosis[39] and more extensive blistering and ulceration[40].

In temporal distribution, the seasonality of HFMD in China shows a spatial pattern that varies significantly from south to north and east to west. HFMD cases can happen all year round, with a high annual incidence in spring or early summer. The annual incidence peaks in June in northern China, while in southern China, there are two peaks per year, one in May-July, and the other is a small peak occurring in September-October[41]. The seasonal epidemiological pattern in Tibet differs from that of other provinces, as the peak incidence of the disease in Tibet is not in spring and early summer but in October each year[42].

5. Factors Affecting CV-A6 HFMD

Studies have confirmed that the incidence of HFMD is closely related to meteorological factors, such as temperature, precipitation, relative humidity, etc. Mean temperature and relative humidity have a significant positive effect on the incidence of HFMD in all climatic zones[43]. The association between temperature and CV-A16 and EV71 showed an inverted U-shape. Meanwhile, EV71 is more likely to

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tolerate high ambient temperatures than CV-A16; therefore, EV71 is more likely to have outbreaks in summer. When the ambient temperature was higher than 11°C, the incidence of CV-A6 and CV-A10 showed an initial consistent positive correlation with temperature[44].SO2 concentration can also increase the risk of HFMD. Still, the mechanism of how exposure to SO2 can increase the risk of HFMD in children is unclear, and it is possible to be related to the stimulation of the respiratory mucous membranes by SO2 and the induction of a systemic immune response[45].

Non-environmental objective factors can also influence the development of CV-A6HFMD. For example, complications at birth, maximum body temperature above 39°C, and first birth increase the risk of severe CV-A6HFMD, whereas breastfeeding and washing hands after play reduce the risk of severe HFMD[41]. A dense population, high prevalence, housing and transport congestion, and shrinking living space are all risk factors that influence the incidence of HFMD, thus contributing to the high prevalence of the disease[46].

The host immune response affects the susceptibility and severity of the disease, and children with the same enterovirus infection will reflect different clinical manifestations, characteristics, and outcomes. This suggests that the patient's innate immunity plays an essential role in influencing childhood HFMD. This genetic influence indicates that host genetic factors may be necessary to determine the degree of infectious disease development. Meng Y et al. found that SNPrs10879355 in the THP2 gene was associated with a high risk of severe CV-A6 HFMD. As a serotonin restriction enzyme in the human brain, TPH2 plays a crucial role in serotonin synthesis in the central nervous system. It follows that. In the pathogenesis of severe CV-A6 HFMD, the serotonin synthesis pathway may be associated with clinical manifestations in the central nervous system[46].

6. Preventive Measures

HFMD is commonly located at the forefront of childhood infectious diseases in China, causing significant damage to children's health, and at present, vaccination is still an effective measure to prevent HFMD. Since 2006, the promotion of EV71 vaccination in many places has led to the effective control of EV71 epidemics, with a significant decrease in the rate of severe illness and mortality, and, at the same time, prompted a change in the dominant pathogenic strain. CV-A6 has become the prevalent dominant strain in the country[47]. Although there is no preventive vaccine or specific therapeutic drug for CV-A6, the successful development of the EV71 vaccine has laid the foundation for developing the CV-A6 vaccine, and many researchers have already achieved particular results.

In the absence of adequate vaccine protection, prevention and control of CV-A6 hand-foot-mouth disease should focus on cutting off the transmission route[48]. For example, it ensures a clean and hygienic environment in public places and effectively isolates infected cases. The source of HFMD is not easy to control, and the transmission route is difficult to eliminate. Protection is given priority to children under the age of five years. Vulnerable groups are imperative, so the most essential measure is to carry out relevant health promotion and education for parents. Simple training of parents' hygiene awareness and disease prevention skills through health education guidance, distribution of publicity materials, and community public welfare lectures is a very effective preventive and control measure[49].

As for the population, the most important means of predicting and reducing outbreaks is epidemiological surveillance[50]. China has established a three-tier laboratory network for HFMD surveillance, which detects and monitors the occurrence of HFMD in real time through pathogen surveillance. This susceptible and effective surveillance network is the basis for preventing and controlling HFMD. This long-term network surveillance has identified two cyclic phases of EV71: an evolutionary branch, C4b, which cycled between 1998 and 2004, and an evolutionary branch, C4a, which has been circulating since 2004[37]. This effective surveillance can guide the diagnosis and treatment of HFMD in the current year by predicting the incidence data from previous years and is an essential tool for early detection and early warning of HFMD activity in China. At the same time, it can provide appropriate guidance for developing HFMD prevention and control programs[51].

7. Summary and Outlook

Since 2008, HFMD has been included in category C infectious diseases for management, and China has attached great importance to HFMD. Since the EV71 vaccination, there has been a significant reduction in severe and fatal cases of EV71 type, and the dominant pathogen has thus shifted. Today, CV-A6 is endemic in many countries and regions of the world and is one of the dominant pathogens causing

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HFMD. Multiple outbreaks of HFMD have occurred due to the change in pathogen serotype and the occurrence of gene recombination. The prevention and control of HFMD in China still needs to be optimistic. Relevant departments should conduct continuous, long-term, systematic, and comprehensive surveillance against HFMD to track its evolutionary characteristics and the pattern and trend of recombinant mutations. Meanwhile, since the EV71 vaccine has no cross-protective effect against CV-A6, it is necessary to invest more in the CV-A6 serotype HFMD vaccine for more comprehensive and in-depth research in the future.

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