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Commentary

Hand foot and mouth disease: Enteroviral load and disease severity

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In this article of *EBioMedicine,* Chunlan Song and colleagues studied 1109 children with hand, foot and mouth disease (HFMD) [1]. They demonstrated that the ones having throat swabs testing positive for a specific enterovirus serotype via RT-PCR had higher viral genomic loads, which correlated with four markers of clinical severity, namely admission to the ICU, CNS complications, LOS over five days and need for IVIG or steroids. This association was significant for patients infected with EV-A71 and less consistent for higher viral genomic loads of CV-A6. The authors observed a decline in viral load over time after illness onset of all HFMD associated enteroviruses. The association was statistically significant for CV-A6, CV-A10 and CV-A4, but not significant for CV-A2, CV-A16, or EV-A71. In the sensitivity analysis, however, the patients whose throat swabs tested negative for enteroviruses but whose stools tested positive for EV-A71 or CV-A16 were included, which allowed detection of a statistically significant difference, which is consistent with the results of previous studies [2]. This is one of the few and the largest investigations to study the association of enterovirus genomic loads among HFMD patients and their clinical severities. It is notable that less than 5% of the children in this study had an underlying medical condition, and none of the patients were immunocompromised.

Enteroviruses are non-enveloped, positive-sense, single-stranded RNA viruses within the *Picornaviridae* family. This family includes more than 100 serotypes: Coxsackieviruses A (CV-A) and B (CV-B); polioviruses; numbered enteroviral serotypes (EV) and echoviruses.

HFMD is generally a benign, self-limited, disease of children, although recent reports show CV-A6 can cause severe disease in adults [3]. Children under five years of age are the group most frequently diagnosed with HFMD due to enterovirus A, e.g. EV-A71, or Coxsackieviruses, e.g. CV-A16, CV-A6 or CV-A10, and rarely by CV-A4, CV-A2 or CV-A8 [4]. Although EV-A71 is responsible for most severe clinical cases, other serotypes have recently been reported to cause an increasing proportion of significant diseases [5,6]. Reports of epidemics of severe HFMD from east Asia have become frequent [5,7].

Generally, HFMD causes only mild clinical signs, e.g. exanthema, and symptoms, e.g. fever, with recovery in a few days. In a minority of cases, however, central nervous system (CNS) symptoms develop, which can progress to cardiopulmonary complications and even death. Long term sequelae of survivors of such symptoms are common, especially following EV-71 infection [4]. Such severe systemic disorders include aseptic meningitis, poliomyelitis-like acute flaccid paralysis, brainstem encephalitis, pulmonary edema and cardiorespiratory collapse.

It is believed that enteroviruses first replicate in the oropharyngeal cavity, especially the tonsils, and the bowel resulting in viremia [7,8], dissemination and replication in mucous membranes and other organs, causing symptoms. Viral invasion of the CNS is rare, but it is thought to occur via migration of the virus along peripheral and cranial nerves to the CNS [9].

Although the findings of the current investigation differ from smaller studies from Vietnam and China, the larger sample size and use of four indicators of clinical severity increase its validity [10]. This observation is especially true for the enteroviral genomic load of EV-A71 and these indicators.

The authors acknowledge several limitations of their findings: 1. Long term sequelae of HFMD, which would be expected to be more frequent and severe in hospitalised patients, were not followed; 2. Quantitative RT-PCR was not used to measure viral load; 3. Throat swabs were only collected at a single time point for each subject; although viral genomic load appeared to decrease over time after symptom onset in throat swabs, collection at multiple time points would have been useful; 4. Although findings from hospitalised patients with HFMD have the most clinical significance, the data may not apply to less symptomatic, non-hospitalised patients.

Although this study and others increase our understanding of the enterovirus-host relationship of HFMD, we have only candidate antivirals for its therapy [7]. Therefore, future studies need to further investigate the pathophysiology of enterovirus infections, comparing hospitalised subjects to less severely affected patients, and follow the long term sequalae. The immune response of HFMD patients also needs better understanding in order to develop more specific antiviral therapies. Recently, two inactivated monovalent EV-A71 vaccines were licensed in China, and a monovalent CV-A16 vaccine and a bivalent EV-A71 and CV-A16 vaccine are under development. International trials, however, are needed to further assess efficacy, safety, durability and cross protection against related enteroviral types.

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Stephen K Tyring wrote the commentary.

Declaration of Competing Interest

No conflicts of interest to declare.

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