

Human Enterovirus 71 Disease in Sarawak, Malaysia: A Prospective Clinical, Virological, and Molecular Epidemiological Study

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Background. Human enterovirus (HEV)-71 causes large outbreaks of hand-foot-and-mouth disease with central nervous system (CNS) complications, but the role of HEV-71 genogroups or dual infection with other viruses in causing severe disease is unclear.

Methods. We prospectively studied children with suspected HEV-71 (i.e., hand-foot-and-mouth disease, CNS disease, or both) over 3.5 years, using detailed virological investigation and genogroup analysis of all isolates.

Results. Seven hundred seventy-three children were recruited, 277 of whom were infected with HEV-71, including 28 who were coinfecting with other viruses. Risk factors for CNS disease in HEV-71 included young age, fever, vomiting, mouth ulcers, breathlessness, cold limbs, and poor urine output. Genogroup analysis for the HEV-71-infected patients revealed that 168 were infected with genogroup B4, 68 with C1, and 41 with a newly emerged genogroup, B5. Children with HEV-71 genogroup B4 were less likely to have CNS complications than those with other genogroups (26 [15%] of 168 vs. 30 [28%] of 109; odds ratio [OR], 0.48; 95% confidence interval [CI], 0.26–0.91; $P = .0223$) and less likely to be part of a family cluster (12 [7%] of 168 vs. 29 [27%] of 109; OR, 0.21; 95% CI, 0.10–0.46; $P < .0001$); children with HEV-71 genogroup B5 were more likely to be part of a family cluster (OR, 6.26; 95% CI, 2.77–14.18; $P < .0001$). Children with HEV-71 and coinfecting with another enterovirus or adenovirus were no more likely to have CNS disease.

Conclusions. Genogroups of HEV-71 may differ with regard to the risk of causing CNS disease and the association with family clusters. Dual infections are common, and all possible causes should be excluded before accepting that the first virus identified is the causal agent.

Since 1997, countries of the Asia-Pacific rim have been affected by large outbreaks of human enterovirus (HEV)-71-associated hand-foot-and-mouth disease (HFMD), which have resulted in hundreds of thousands of cases and many deaths [1–7]. HFMD is a common exanthema of young children, characterized by fever, rash on the palms and bottoms of the feet, and ulcers in the oral cavity. Most patients have mild

cases of disease, but some patients develop severe neurological complications (i.e., aseptic meningitis, acute flaccid paralysis, and encephalitis) or systemic disease (i.e., shock and cardiac dysfunction). HFMD is caused by enteroviruses (genus *Enterovirus*, family Picornoviridae), particularly Coxsackie A virus (CAV)-10, CAV-16, and HEV-71, which are mostly transmitted by the fecal-oral route. Phylogenetic studies have divided HEV-71 strains into genogroups A, B, and C, which have been further subdivided [4, 8–10]. The incidence of CNS disease and other severe complications appears to have varied among outbreaks of HEV-71 infection. The reason for this is unclear, but differences between genogroups [10–12] and coinfection with other viruses, such as a newly characterized adenovirus [1, 13], have been postulated. However, comparisons between outbreaks have been hampered by the retrospective nature

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