Neonatal hand, foot, and mouth disease: a case-control study in Shanghai

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Abstract

Background Evidence of hand, foot, and mouth disease (HFMD) in neonates is limited. This study aimed to report the clinical symptoms, possible transmission routes, and prognosis of neonatal HFMD in Shanghai.

Methods This was a case-control study based on registry system of HFMD. All neonates and infected family members were enrolled between 2016 and 2017 in Shanghai. Neonates with HFMD were followed for at least half a year. The detailed questionnaires, medical history and physical examination were recorded. Routine blood examination, liver and renal function, immunophenotypes of peripheral blood lymphocytes (CD3, CD4, and CD8 T-cells; NK cells), immunoglobulin (Ig) M, IgG, and IgA and cytokine interleukin (IL-1β, IL-2R, IL-6, IL-8, IL-10, and TNF-α) levels were detected. All rectal swab specimens were collected and genotyped for enterovirus. T-test or nonparametric test was used to evaluate the differences. Logistic analysis was applied to find the risk of clinical symptoms in the group of neonates and their HFMD paired siblings.

Results There were 16 neonates among the 12608 diagnosed patients with HFMD, accounting for 1.3‰. All the neonates were transmitted within-family, mainly by the elder sibling, with different types of coxsackievirus A6 infection. Coxsackievirus A6 was also the emerging and predominant causative agent of HFMD in Shanghai. None of the neonates with HFMD suffered fever, onychomadesis, or severe complications. However, two elder sibling patients showed lethargy, and one developed hypoperfusion. The white blood cells in the elder siblings with HFMD were generally higher than the neonates with HFMD. The immunologic function of the neonates was basically normal. The inflammatory response was high regardless of the neonates or elder siblings. The clinical symptoms receded at about one week. None of the neonates had sequelae.

Conclusions The severity of neonates infected with HFMD may vary with pathogen. With
the two-child policy in China, it should be noticed that elder siblings may be the main route of HFMD transmission.

Introduction

Hand, foot, and mouth disease (HFMD) is one of the most recognizable viral exanthems in children and adults [1]. In March 2008, a sudden outbreak of HFMD occurred in Anhui Province, China. In May, HFMD was defined as a C-class notifiable disease. The incidence of HFMD is ranked first place among various communicable diseases since 2009 and has become an important public issue [2, 3]. HFMD is generally a mild clinical syndrome [4, 5]; however, sometimes, serious complications may occur [6]. Although the range of HFMD onset age is quite wide, from neonate to 70 years old, children aged 5 years and younger are the most susceptible to HFMD and may develop severe clinical symptoms [7, 8]. It was reported that an age younger than 3 years shows an increased risk of severe HFMD [2, 8]. However, until now, the age-specific risk of severe HFMD in young children is not well studied. The biological mechanism regarding why young HFMD shows more progressive remains unclear.

Neonates are the youngest children. Thus far, three case reports have been published on 8 cases of neonatal HFMD [9-11]. One case reported on neonatal enterovirus 71 (EV71) infection and another on coxsackievirus (CV) B3 infection in 2014, with both cases progressing to severe HFMD. Another report in 2017 mentioned five benign neonatal cases without associated pathogen. In this prospective cohort study, we recruited the neonates with HFMD and their families in Shanghai, 2016-2017, and explored the epidemiological features, clinical presentations, pathogens, and immune function of neonatal HFMD compared with normal neonatal controls and their paired siblings.

Materials And Methods


**Participants and specimens**

The Chinese government established a network-based national surveillance system for HFMD since 2009. In Shanghai, local health providers and physicians are required to report clinically diagnosed HFMD cases to the Shanghai Municipal Centre for Disease Control and Prevention (CDC) within 24 hours via the surveillance system. Basic epidemiologic and clinical information was recorded for each HFMD patient \[12\]. Sixteen local CDC representing 16 districts are responsible for collecting samples and transporting them in their own districts. However, the vast majority of children with HFMD are treated in two designated hospitals, the Children’s Hospital of Fudan University and the Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine. The specimens of patients were sampled for pathogen test at local sentinel hospitals in each district, at least ten outpatients diagnosed with HFMD per month. The clinicians can also test the specimens as the condition requires. Throat swabs or/and faecal samples (rectal swabs) are then sent directly to microbiology labs at the local CDCs, where EV71, CV-A16, CV-A6, CV-A10 and other EV can be confirmed by real-time PCR \[13\].

All cases were diagnosed according to the criteria of HFMD Prevention and Treatment Guidelines \[14\]. Patients who had a rash, with or without fever, and no other organ damage, were classified as having common HFMD. Those with any complications (i.e., aseptic meningitis, brainstem encephalitis, encephalitis, encephalomyelitis, acute flaccid paralysis or autonomic nervous system dysregulation, pulmonary edema, pulmonary hemorrhage, or cardiorespiratory failure), or those who died, were classified as having severe HFMD. From January 2016 to December 2017, 12608 patients were diagnosed with HFMD at Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine. The distribution of the patients covered all 16 municipal districts in Shanghai. Patients who met the following criteria were recruited in our study: 1. neonates diagnosed
less than 28 days after birth; 2. skin lesions were manifest as small vesicles, papulovesicular lesions or macular rashes on the palms, soles, buttocks and oral mucosas, or presenting on the limbs, trunks or facial areas. All of the family members were also included for screening. Because the prognosis of neonatal HFMD is unknown, they were all admitted to the hospital for observation, including routine clinical blood examination, biochemical function, immune function, and virus detection. Infected family members were also fully evaluated and treated. The clinical specimens (e.g., rectal swabs and plasma) were collected from each patient within one days of diagnosis. To compare the differences of immunological function, we also recruited age- and birth weight-matched non-infected neonates (e.g., breast milk jaundice) as neonatal controls, the age-matched preoperative patients without infection (e.g., hypospadias) as elder sibling’s controls. Finally, 16 neonates with HFMD and their infected families were included, and all of them were followed up for at least six months for sequelae.

This study was approved by the Ethics Committee of Xinhua Hospital, affiliated to Shanghai Jiao Tong University School of Medicine (XHEC-C-2018-082), and the procedures were carried out in accordance with the Helsinki Declaration. Parents or guardians of each subject were required to sign a written informed consent form.

**Data collection**

Demographic data, clinical manifestations, and laboratory findings of every participant were recorded. Among the clinical manifestations, fever, timing of skin lesions, and distribution of skin lesions were evaluated. The skin lesions were classified into 8 sites: peri-nasal, peri-oral, scalp, palms/soles, lower limbs, upper limbs, abdomen and intraoral lesions.

Complete blood cell count, liver and kidney function, and the levels of myocardial enzymes, immunoglobulins, lymphocyte subsets, and cytokines were assessed in each
case and control. The immunophenotypes of peripheral blood lymphocytes (CD3, CD4, and CD8 T-cells; NK cells) were determined by flow cytometry (Becton Dickinson Immunocytometry Systems) and were analysed by Cell Quest software (Becton Dickinson). The serum levels of immunoglobulin (Ig) M, IgG, and IgA were detected by turbidimetric immunoassay. ELISA for quantitative determination (Quantikine; R&D Systems) was used to analyse the levels of cytokines (IL-1β, IL-2R, IL-6, IL-8, IL-10, and TNF-α). The assays were performed according to the manufacturer's instructions.

The rectal swab specimens from each patient were genotyped for enterovirus. Viral RNA was extracted directly from clinical specimens using a QIAamp Viral RNA Mini Kit (Qiagen, Santa Clara, CA) and was stored at -80 °C. The identification of EV and serotyping of EV71 and CV-A16 from samples were performed by real-time reverse transcription-polymerase chain reaction (RT-PCR) as previously described [15, 16]. To further identify EV serotypes other than EV71 and CV-A16, semi-nested RT-PCR and sequencing were conducted as previously described [17]. The serotype was determined by comparison of the viral sequences with corresponding sequences of the EV prototype strains using blast online (https://blast.ncbi.nlm.nih.gov/ Blast.cgi).

Statistical analysis

We calculated the means and their standard deviations of normal distributed variables and medians (interval of quartiles) of skewed distributed variables. T-test was used only if it was normally distributed, and the nonparametric test were applied for those abnormally distributed when pair-wise comparisons were made. The cytokine levels all showed abnormal distributions; thus, they were log-transformed into normal distributions in the t-test analysis. Frequency and percent values were calculated for categorical variables, and chi-square test was used to test the difference in the categorical variables between the neonatal HFMD and paired sibling HFMD. Logistic analysis was applied to identify the risk
of clinical symptoms in these two groups. All statistical analyses were conducted using SPSS 17.0 software. P-value <0.01 was regarded as statistically significant.

Results

Clinical presentations of the neonates with HFMD

There were 16 neonates among the 12608 diagnosed cases with HFMD at Xinhua Hospital affiliated to Shanghai Jiao Tong University in Shanghai 2016-2017, accounting for 1.3‰. Among them, there were 14 cases of severe HFMD, and most of which were EV71 infection. A total of 259 patients were sampled from this sentinel hospital for routine enterovirus surveillance, among which 206 cases were positive, with a positive rate of 79.54%. CV-A6 was the predominant causative agent of HFMD (Figure 1). All of the neonatal cases were not severe, while two elder siblings developed severe HFMD cases. Half of the neonates with HFMD were diagnosed in the summer.

The median age of the neonates with HFMD was 25 days, ranging from 21 to 27 days. All the neonates were full term with a normal birth weight. The median age of their elder siblings was 4.1 years with a range of between 2.4 years and 6.3 years. Among them, 37.5% of neonates and 62.5% of elder siblings were boys. As shown in Table 1, the symptoms of neonates with HFMD cases were milder than their elder siblings. None of the neonates developed complications of hypoperfusion, lethargy, onychomadesis, or other complications. Most of the elder siblings had fever, whereas none of the neonates did. Ten elder sibling patients had vomiting symptoms, two had lethargy, and one developed hypoperfusion. The prevalence of vomiting was 5 times higher in the elder siblings than in the neonates. Cutaneous lesions were more common in elder siblings than in neonatal cases, especially intraoral erosions. The site of the rash of neonate cases was not typical, mainly in the peri-oral and upper limb (Figure 2). After symptomatic treatment, the clinical symptoms receded at about one week, and no sequelae occurred within half a year.
Interestingly, all infected neonates had an elder sibling affected, and two parents in the 16 families had oral herpes excluded herpes simplex virus infection.

**Laboratory findings**

On comparison of complete blood cell count (Table 2), we found that the WBC count in the elder siblings with HFMD was higher than that in the age-matched controls, but that in the neonate with HFMD was not. The median (25\textsuperscript{th}-75\textsuperscript{th} percentile) of WBC count in neonatal HFMD was $8.5 \times 10^9$/L, and the median neutrophil ratio was $26.6 \times 10^9$/L. No statistically significant differences were found in liver function, kidney function and cardiac enzyme series between cases and controls, either in neonates or their elder siblings.

Regarding immune function, as shown in Table 3, the levels of inflammatory markers such as IL-1\textbeta, IL-2R, IL-6 and TNF-\alpha were all higher in the cases, in both the neonates and their elder siblings (P <0.01). The levels of IgA and IgM were higher in the elder-sibling patients than that in the neonates, which may be due to age-related immunological development. The immunoglobulin levels were normal in the neonates with HFMD; however, the level of CD8 T-cells was decreased. The neonate cases exhibited a median CD8 T-cell count of $534.0 \times 10^9$/L, and the control group exhibited a median CD8 T-cell count of $970.0 \times 10^9$/L (P <0.01). There were no significant differences in other T cells in all groups.

By aetiological detection, we found all cases were infected with CV-A6 (CV-A6/P619/2013/China capsid protein, P2 protein, CV-A6/P477/2013/China capsid protein, P2 protein, CV-A6/P471/2013/China capsid protein, P2 protein, CV-A6/P424/2013/China capsid protein, P2 protein). The viral genotypes were the same within the family, suggesting the homogeneity of the infection in the family.
Discussion

Neonatal HFMD is rarely reported in the literature. In this study, we found the percent of neonatal HFMD among all cases was only 1.3‰ in Shanghai, 2016-2017. All 16 neonates were infected within families, mainly from their elder siblings. They were diagnosed with different subtypes of CV-A6 infection aetiologically. Neonatal HFMD cases showed normal immune function. Almost all plasma levels of cytokines were significantly higher in cases than in their controls.

HFMD is a common acute enterovirus infection, characterized by a short-lasting fever, mouth ulcers, and vesicles on the hands, feet, or hips [18]. It can be transmitted both horizontally (fecal-oral/respiratory route) and vertically (prenatal infection). Most newborns presenting with serious enterovirus disease acquire the infection from a symptomatic mother in the perinatal period; up to 60 percent of mothers of infected infants report a febrile illness during the last week of pregnancy [19]. Additionally, serious enterovirus disease is also acquired via nosocomial transmission, with spread throughout nurseries occurring via caregivers engaged in mouth care, gavage feeding, and other activities requiring direct contact. Close contact with infected family members or caregivers is also an important route of transmission. In our study, the age range of neonatal onset was 19-28 days, and the mothers had no prenatal infection symptoms, so vertical transmission is not considered. In China, mothers traditionally are expected to rest indoors for one full month after giving birth and avoid contact with people outside the family, so the infection chances are very low for mothers. With the adoption of the two-child policy, the potential of cross contamination is very high for elder siblings, who are generally pre-schoolers in kindergarten [20]. In addition, according to the epidemiological investigation, there were children in the family infected earlier than the neonates, and the pathogen was the same epidemic strain, so it is speculated that neonatal cases are mainly
transmitted by the family. However, it’s still hard to verify the transmitted pathway. Systemic enterovirus diseases in the new-born typically occur some characteristic clinical syndromes, such as myocarditis or fulminant hepatitis, and are well-known causes of neonatal sepsis and viral meningitis [21]. The National Enterovirus Surveillance System in the United States reported 26,737 EV detections during 1983-2003, and neonates accounted for 2544 (11.4% of those with known age) [22]. The genus enterovirus includes four species of enterovirus (A-D) known to infect humans. CV-A16 and EV71 were the serotypes most frequently associated with HFMD and were responsible for most of the large outbreaks [23]. Among healthy individuals, 50.49% and 54.23% had positive neutralising antibodies against EV71 and CV-A16, respectively in Shanghai [13]. In Ho Chi Minh City, Viet Nam, approximately 50% of neonates were found to have detectable EV71-neutralizing antibodies [24]. It was surmised that the antibodies existing in the neonatal blood from maternal blood and breast milk, declining with age, might provide protection against the infection [25]. It was hypothesized that the lack of protective antibodies in younger children may account for the high incidence and case-fatality rate [24]. The outcome of neonatal infection is strongly influenced by the presence or absence of passively acquired maternal neutralizing antibodies. Beginning in 2008, CV-A6 has been increasingly reported as a cause of outbreaks of HFMD around the world, and it may also be associated with more severe disease than typical HFMD [4, 26-32]. It was reported that sporadic cases and epidemics in patients with CV-A6 appear, principally affecting elder children, adolescents, and adults rather than young infants. CV-A6 has replaced EV71 and CV-A16 as the most common pathogen causing HFMD in Shanghai [12]; thus, we inferred that most pregnant women had been infected asymptomatically, but the proportion of detected neutralizing antibodies in maternal blood was too low to protect their child. In the literature, significant clinical differences were reported in the HFMD depending on
the pathogen. Genetic typing to distinguish the exact virus strain is usually not necessary to confirm the HFMD diagnosis. However, in some cases of HFMD, information on the exact type of the virus is crucial for appropriate disease management and reliable assessment of the risk of potential complications. The sole published EV71 infection neonate case was quite severe. Another reported CV-B3, which was not fatal and was a self-limited pathogen in children, also caused severe conditions in a neonate case. However, none of the five neonates clinically diagnosed with HFMD developed brainstem encephalitis or pulmonary oedema, and they all recovered well in southeast China. CV-A6 had a broader spectrum of manifestations [33]. In our study, the symptoms of neonate HFMD cases were mild. The risk of neonate cases with symptoms of fever, vomiting, and onychomadesis was lower than that for elder children. They may have an atypical skin presentation with facial involvement and vesiculobullous lesions on the body.

Immunology reaction may be important to HFMD. Almost all the fatal HFMD cases had symptoms of autonomic nervous system dysregulation and increased sympathetic discharge, indicating the involvement of reticular formation. Immune activation, such as higher levels of cytokines and WBC, were the early biomarkers to measure the condition of the autonomic nervous system. In our study, the levels of these biomarkers were increased in both neonatal and elder sibling patients. However, neonatal HFMD showed a significantly lower CD8 T-cell count, which was not uncommon in acute viral infection. The T-cell subset assay is an accurate method to evaluate cellular immunity, with abnormal results indicating a higher risk of occurrence and aggravation of viral diseases. Regarding the CD T-cell series of HFMD in children, wang and colleagues found that CD4 T-cells, CD8 T-cells, and NK cells were depleted in patients with pulmonary edema, which might impair the clearance of EV71 [34]. Another study had found that CD4 T-cell decreased while CD8 T-cell showed no change [35]. There are few reports on neonatal HFMD. We speculate that
the low level of CD8 T-cell may be related to the sampling time. Although the samples were taken upon admission, there may be a delay in the onset at home and the appearance of a few rashes. Because the sample is based on the symptomatic population, there may be selection bias. In addition, some results, such as why the level of CD8-T cell is low, need to be confirmed by further studies.

Conclusions

Neonatal HFMD caused by CV-A6 shows mild clinical symptoms and basically normal immune dysfunction. Neonatal HFMD is not necessarily very serious, and the severity of the disease may be related to the pathogen. In China, where the two-child policy is gradually being adopted, the brother or sister is the main source of infection. If there is infection, infection-control measures should be in place.

Declaration

Ethics approval and consent to participate:

This study was approved by the Ethics Committee of Xinhua Hospital (XHEC-C-2018-082), and the procedures were carried out in accordance with approved guidelines.

Consent for publication:

Not applicable.

Availability of data and material:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:
LH and WZ had the idea for the study, designed and revised the manuscript. SX and HL were major contributors in writing the manuscript. GX, DZ, XL, YH and YQ collected the data. PQ and WZ detected the pathogen. XZ analyzed data. All authors read and approved the final manuscript.

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Tables
Table 1. Clinical features of neonates and paired older siblings with hand, foot, and mouth disease

| Clinical features                        | Neonate (N = 16) | Older siblings (N = 16) | P-value | Odds ratio |
|------------------------------------------|-------------------|------------------------|---------|------------|
| Fever (temperature $\geq 39 ^\circ C$)   | 0                 | 14 (87.50)             | $< 0.01^a$ | 0 (0.0, 0.08) |
| Vomiting                                 | 2 (12.50)         | 10 (62.50)             | $< 0.01^*$ | 0.20 (0.05, 0.77) |
| Seizure                                  | 0                 | 0                      | 0.50     | 1.00 (0.14, 7.7) |
| Symptom of hypoperfusion                 | 0                 | 1 (6.25)               | 0.50     | 0 (0.0, 19.0) |
| Lethargy                                 | 0                 | 2 (12.50)              | 0.24     | 0 (0.0, 3.42) |

Cutaneous areas affected

| Area           | Neonate (%) | Older siblings (%) | P-value | Odds ratio |
|----------------|-------------|--------------------|---------|------------|
| Peri-nasal     | 4 (25.00)   | 3 (18.75)          | 0.69    | 1.43 (0.24, 9) |
| Peri-oral      | 13 (81.25)  | 14 (87.50)         | 0.33    | 0.93 (0.69, 1) |
| Scalp          | 0           | 0                  | 0.50    | 1.00 (0.14, 7.7) |
| Palms/soles    | 6 (37.50)   | 13 (81.25)         | 0.02    | 0.41 (0.20, 0.7) |
| Lower limbs    | 2 (12.50)   | 9 (56.25)          | 0.01    | 0.27 (0.08, 0.7) |
| Upper limbs    | 14 (87.50)  | 13 (81.25)         | 0.66    | 1.30 (0.42, 4) |
| Abdomen        | 0           | 1 (6.25)           | 0.50$^a$ | 0 (0.0, 19.0) |
| Intraoral      | 10 (62.50)  | 16 (100.00)        | $< 0.01^*$ | 0.38 (0.24, 0.7) |
| Onychomadesis  | 0           | 5 (31.25)          | 0.02    | 0 (0.0, 0.69) |
| Complications  | 0           | 1 (6.25)           | 0.50$^a$ | 0 (0.0, 19.0) |

$^a$Two-tailed exact P-value.

$^b$Conditional maximum likelihood estimate of odds ratio.

*Statistical significance.

Table 2. Routine blood test of neonates and paired older siblings with hand, foot, and mouth disease

| Parameter                  | Neonate HFMD      | Neonate control    | $P$-value$^1$ | Older-sibling |
|----------------------------|-------------------|--------------------|---------------|---------------|
| WBC count ($\times 10^9$/L) | 8.5 (4.2, 12.8)   | 7.1 (5.5, 9.8)    | 0.51          | 15.5 (6.4, 2.2) |
| RBC count ($\times 10^{12}$/L)| 4.3 (3.2, 5.1)   | 4.1 (3.3, 4.6)    | 0.20          | 4.3 (3.5, 5.5) |
| Platelet count ($\times 10^9$/L)| 378.5 (164.6, 406.9)| 349.0 (248.5, 398.0)| 0.01          | 283.1 (233.7) |
| Leukomonocyte (%)          | 53.4 (24.8, 76.4) | 54.6 (43.7, 61.4) | 0.84          | 47.2 (30.5, 6) |
| Monocyte (%)               | 11.2 (9.4, 14.7)  | 9.7 (7.8, 11.7)   | 0.12          | 10.3 (7.9, 17) |
| Neutrophil (%)             | 26.6 (19.2, 49.2) | 22.0 (13.7, 34.2) | 0.48          | 38.6 (13.2, 7) |
| Haemoglobin (g/L)          | 103.2 (89.7, 118.1)| 140.0 (107.0, 154.5)| 0.05           | 118.1 (101.3) |

$P$-value$^1$: T-test between neonate HFMD and neonate control.

$P$-value$^2$: T-test between older HFMD and age-compared control.

$P$-value$^3$: T-test between neonate HFMD and older-sibling HFMD.

*Statistical significance.
| Parameter                  | Neonate HFMD            | Neonate control         | P-value<sup>1</sup> | Older-sibling HFMD | P-value<sup>2</sup> |
|---------------------------|-------------------------|-------------------------|---------------------|--------------------|---------------------|
| CD3 T-cell                | 2837.2 (2243.3, 3982.1) | 3536.3 (3196.6, 4450.2) | 0.01                | 221                |
| CD4 T-cell                | 2161.6 (1845.8, 4132.7) | 2488.5 (2165.5, 3379.0) | 0.48                | 122                |
| CD8 T-cell                | 534.0 (314.2, 824.6)    | 970.0 (904.5, 1150.5)   | < 0.01*             | 911                |
| CD16+CD56+ (NK cell)      | 250.3 (123.9, 325.4)    | 361.0 (239.5, 478.5)    | 0.72                | 573                |
| IgG                       | 3.2 (2.3, 4.1)          | 6.2 (5.2, 7.0)          | 0.68                | 9.7                |
| IgA                       | < 0.3                   | < 0.3                   | 1                   | 2.0                |
| IgM                       | 0.4 (0.2, 0.6)          | 0.2 (0.2, 0.3)          | < 0.01*             | 2.5                |
| IL-1β                     | 730.1 (384.8, 937.5)    | 61.9 (22.5, 71.5)       | < 0.01*             | 101                |
| IL-2R                     | 1516.4 (497.3, 2732.3)  | 1438.5 (1277.5, 1556.5)| < 0.01*             | 139                |
| IL-6                      | 32.4 (28.2, 67.3)       | 3.8 (3.1, 48.4)         | < 0.01*             | 16.6               |
| IL-8                      | 63.6 (14.6, 1283.6)     | 110.8 (19.7, 1866.0)    | < 0.01*             | 58.3               |
| IL-10                     | 26.4 (14.2, 46.8)       | 17.5 (12.3, 53.1)       | 0.01                | 79.3               |
| TNF-α                     | 15.3 (9.5, 38.2)        | 13.2 (11.0, 26.7)       | < 0.01*             | 18.6               |

P-value<sup>1</sup>: T-test between neonate HFMD and neonate control.
P-value<sup>2</sup>: T-test between older HFMD and age-compared control.
P-value<sup>3</sup>: T-test between neonate HFMD and older-sibling HFMD.
*Statistical significance.

Figures
Figure 1

Enterovirus-positive HFMD cases, 2016-2017.
Figure 2

A 22-day-old boy with CV-A6 infection showing vesicles on his upper limb