# Dermatological Spectrum of Hand, Foot and Mouth Disease from Classical to Generalized Exanthema

*Thomas Hubiche, MD,* Isabelle Schuffenecker, MD, PhD,† Franck Boralevi, MD, PhD,‡ Christine Léauté-Labrèze, MD,‡ Laure Bornebusch, MD,§ Christine Chiaverini, MD, PhD,¶ Alice Phan, MD,‖ Annabel Maruani, MD, PhD,** Juliette Miquel, MD,†† Marie-Edith Lafon, MD, PhD,‡‡ Bruno Lina, MD, PhD,† and Pascal Del Giudice, MD,* on behalf of the Clinical Research Group of the French Society of Pediatric Dermatology (Groupe de recherche clinique de la société française de dermatologie pédiatrique).*

**Background:** Hand, foot and mouth disease (HFMD) is classically defined as a childhood fever accompanied by a rash with vesicles or erosions of the oral mucosa, hands, feet and sometimes the buttocks. Severe neurological complications are associated with enterovirus 71 outbreaks in Asia. Recently, it has been suggested that HFMD is related to coxsackie virus A6 (CV-A6) when there is an atypical rash. The objective of the study is to determine the dermatological pattern of HFMD and to identify the virus serotypes associated with a specific dermatological pattern.

**Methods:** A prospective, cross-sectional study was conducted in 7 pediatric dermatology units in France from March 2010 to February 2012. All children with clinically suspected diagnosis of HFMD were included. Clinical data were collected and swabs from the nasopharynx and vesicles were taken for reverse transcription polymerase chain reaction and genotyping. Only children with confirmed HFMD—defined by clinical diagnosis of HFMD and positive enterovirus polymerase chain reaction results—were included for analysis.

**Results:** One hundred and four children consulted for suspected HFMD, including 89 (mean age: 25.7 months; sex ratio M/F 1.54) with confirmed HFMD. Seventy-eight (87.6%) had skin lesions on sites other than hand, feet and mouth. Thirty-seven (41.5%) had 5 or more anatomical sites involved (hand, feet and mouth, buttocks, legs, arms and trunk) considered as widespread exanthema. Widespread vesicular exanthema was observed with both CV-A6 and CV-A16. Peri-oral rash was associated with CV-A6 ($P < 0.001$).

**Conclusions:** HFMD has a clinical spectrum ranging from classical to generalized vesicular exanthema. Generalized and atypical exanthema were observed with both CV-A6 and CV-A16 infections. CV-A6 is associated with peri-oral rash.

**Key Words:** human enterovirus, coxsackie virus, hand, foot, and mouth disease, vesicular exanthema

(*Pediatr Infect Dis J* 2014;33:e92–e98)

Accepted for publication October 9, 2011.

From the *Unité de Dermatologie Infectiologie, CHI Fréjus Saint Raphaël, Fréjus; †Centre National de Référence des Entérovirus, Laboratoire de Virologie Est des Hospices Civils deLyon, Groupement Hospitalier Est, Bron cedex; ‡Unité de Dermatologie pédiatrique, Centre de référence maladies rares de la peau, Hôpital Pellegrin-Enfants, CHU de Bordeaux, Bordeaux; §Service de Pédiatrie, CHG Grasse, Grasse; ¶Consultations de pédiatrie, hopitaux pediatriques CHU-Lenval, Service de Dermatologie, Hôpital Archet II, CHU de Nice, Nice; ‖Unité de Dermatologie Pédiatrique, Hôpital Femme Mère Enfant, CHU Lyon, Bron; **Service de dermatologie, Hôpital Trousseau, Université François Rabelais, Tours; ††Service de Dermatologie, CHU Pontchaillou, Rennes; and ‡‡Département de Virologie et d'Immunologie Biologique and Laboratoire EA 2968, Centre Hospitalo-Universitaire de Bordeaux, Bordeaux, France.

The authors have no funding or conflicts of interest to disclose.

Address for correspondence: Thomas Hubiche, MD, Unité de Dermatologie Infectiologie, CHI Fréjus Saint Raphaël, 240 avenue de Saint Lambert, 83600 Fréjus, France. E-mail: Hubiche-t@chi-frejus-saint-raphael.fr.



ISSN: 0891-3668/14/3304-0e92
DOI: 10.1097/INF.0000000000000120

Hand, foot and mouth disease (HFMD) is caused by certain human enteroviruses (EV). Clinical signs are usually benign except those related to enterovirus 71 (EV-71) associated with significant morbidity and mortality in children.[1] The typical clinical manifestations of HFMD include fever accompanied by vesicles or erosions limited to the oral mucosa, hands, feet and sometimes the buttocks. However, according to the few clinical studies performed,[2–4] typical anatomical sites vary. Other dermatological manifestations such as peri-oral rash and onychomadesis have also been reported.[5–7] Recently, it has been suggested that HFMD related to coxsackie virus A6 (CV-A6) has a more intense and widespread rash.[8–13] This atypical HFMD manifestation could be mistaken for other infections.[12] Clinical studies of HFMD describing dermatological manifestations are rare. They have been conducted mainly in an epidemic context, related to 1 serotype and are based mainly on retrospective dermatological assessment. The purpose of this study was to describe the dermatological features of HFMD, not in an epidemic context, and to identify the potential clinical specificities associated with the virus serotypes.

## PATIENTS AND METHODS

This cross-sectional study was conducted from March 1, 2010, to February 28, 2012, in 7 pediatric dermatological units in France (Unité de Dermatologie Infectiologie, CHI Fréjus Saint Raphaël; Unité de Dermatologie Pédiatrique, CHU Bordeaux; Service de Pédiatrie, CHG Grasse; Service de Dermatologie, CHU Nice; Unité de Dermatologie Pédiatrique, CHU Lyon sud; Service de Dermatologie, CHU Tours and Service de Dermatologie, CHU Rennes).

### Inclusion Criteria

All patients aged <18 years who were seen for suspected HFMD were enrolled in the study. Informed consent was obtained from accompanying parents. HFMD was suspected on the basis of the clinical diagnosis of an experienced clinician and defined by the presence of papulo-vesicular lesions in at least 2 classical anatomical sites, namely hand, foot and mouth (HFM). All suspected cases submitted nasopharyngeal swabs (Σ-virocult, Corsham, Wiltshire, England) and vesicular fluid swabs, when possible. These swabs were used for virological analysis. A case was confirmed as HFMD when the enterovirus polymerase chain reaction (PCR) was positive on at least 1 swab.

### Clinical Assessment

All patients were examined by a senior pediatric dermatologist among the authors. The disease history and clinical findings were recorded on a standardized form (Appendix 1). To assess the severity of the skin lesion, a clinical score ranging from 2 to 7 was given according to the number of anatomical sites involved (mouth, peri-oral, hands, feet, buttocks, trunk,

legs, arms). Children with lesions at 5 or more anatomical sites were considered to have widespread exanthema. After obtaining oral consent, photographs of clinical lesions were taken. These were analyzed by 2 dermatologists (T.H. and P.D.G.) to validate the clinical assessment and identify potential atypical manifestations.

## Virological Analysis

Swabs from nasopharyngeal secretions and skin vesicle fluid were sent to the National Reference Laboratory Center for Enterovirus (Lyon, France) for analysis. Only EV detection was performed using real-time reverse transcription PCR using the Smart EV assay (Cepheid) on the Smart Cycler 2. For genotyping, the partial VP1 coding sequence was determined using the nested PCR assay described by Nix et al[14] and compared with homologous sequences by Blast and phylogenetic analysis. When different serotypes were identified from nasopharyngeal and skin vesicle samples, the serotype identified from the vesicle sample was considered to be responsible for HFMD symptoms.

## Ethics

Oral informed consent was obtained from accompanying parents. Approval by the institutional and ethical review board was requested. However, we found that approval by the institutional and ethical review board is not required for observational studies in France.

## Statistical Analysis

Discrete variables were expressed as counts (percentage), continuous variables were expressed as means ± standard deviation. Variations between groups were evaluated using analysis of variance (T test) for age, temperature and clinical score. Differences for discrete variables (clinical characteristics) were analyzed using the $\chi^2$ test or Fisher's exact test. $P \leq 0.05$ was considered to be statistically significant.

# RESULTS

From March 1, 2010, to February 28, 2012, 104 children were enrolled from 7 dermatological pediatric units (Fréjus: n = 43; Bordeaux: n = 31; Grasse: n=14; Lyon, n = 6; Nice: n = 6, Tours: n = 3 and Rennes: n = 1). EV detection was positive in 89 (85.6%) patients. Their mean age was 25.7 months (range: 3–216 months) and M/F sex ratio was 1.54 (Table 1).

## Clinical Manifestations

Only the EV-positive patients were included. Fifty-nine patients (66.3 %) had skin lesions in the 3 bastion areas (HFM). However, 78 children (87.6%) had skin lesions elsewhere. The areas involved were mainly the buttocks (67.4%), legs (56.2%), arms (25.8%) and trunk (20.2%; Table 1). None had lesions on the scalp. Thirty-seven children (41.5%) with confirmed HFMD had 5 or more anatomical sites involved and 11 (12.3%) had only 2 sites (Fig. 1). The average number of anatomical sites involved was 4.5 (Table 1).

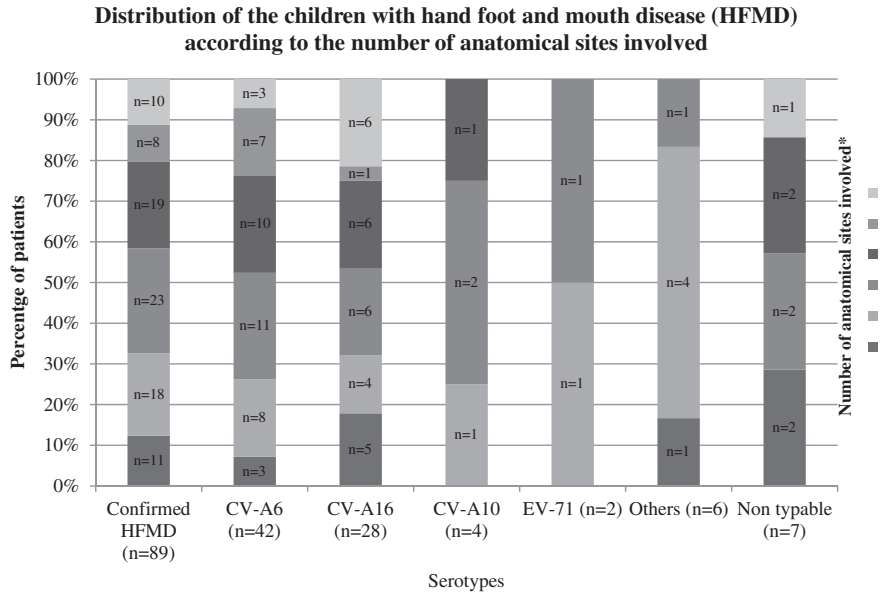
**TABLE 1.** Clinical Characteristics of the 89 Confirmed HFMD

| | | Enterovirus Serotypes | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Enterovirus Positive (n = 89) | CV-A6 (n = 42) | CV-A16 (28) | *P* value* | CV-A10 (n = 4) | EV-71 (n = 2) | Others (6) | Untypables (n = 7) |
| Age (months) | 25.7 (26.3) | 22.8 (13.8) | 28,6 (38.8) | 0.37 | 46.7 (51.7) | 28,5 (17.7) | 14.0 (3.1) | 28.1 (12.9) |
| Male female ratio | 1.54 | 1.2 | 3 | 0.86 | 1 | 0 | 2 | 1,3 |
| Epidemic context | 36 (40.4) | 21 (50) | 11(39.3) | 0.62 | 3 (75) | 0 | 1 (16.6) | 2 (28.5) |
| Within family | 20 (22.5) | 8 (19.0) | 6(21.4) | 0.80 | 3 (75) | 0 | 1 (16.6) | 2 (28.5) |
| School day care | 19 (21.3) | 13 (30.9) | 5(17.9) | 0.22 | 0 | 0 | 0 | 0 (0) |
| Fever at enrollment | 37.7 (1.0) | 37.8 (1.0) | 37.4 (0.8) | 0.11 | 37.6 (1.5) | 38.4 (2.0) | 38.0 (0.9) | 38.2 (1.3) |
| Cutaneous signs | | | | | | | | |
| Hands | 81 (91.0) | 3 (85.7) | 26 (92.8) | 0.30 | 4 (100) | 2 (100) | 6 (100) | 7 (100) |
| Foot | 73 (82.0) | 33 (78.5) | 24 (85.7) | 0.45 | 4 (100) | 2 (100) | 4 (66.6) | 6 (85,7) |
| Buttock | 65 (73.0) | 34 (80.9) | 20 (71.4) | 0.35 | 3 (75.0) | 0 (0.0) | 4 (66.6) | 4 (57.1) |
| Oral ulcer | 62 (69.7) | 28 (66.6) | 22 (78.6) | 0.28 | 4 (100) | 2 (100) | 2 (33.3) | 4 (57.1) |
| Legs | 54 (60.7) | 29 (69.0) | 19 (67.8) | 0.91 | 1 (25.0) | 1 (50.0) | 0 (0.0) | 4 (57.1) |
| Peri-oral | 46 (51.7) | 29 (69.4) | 5 (17.8) | <0.001 | 3 (75.0) | 1 (50.0) | 3 (50.0) | 5 (71.4) |
| Arm | 27 (33.3) | 14 (33.3) | 11 (39.3) | 0.61 | 1 (25.0) | 0 (0.0) | 0 (0.0) | 1 (14.3) |
| Trunc | 20 (22.5) | 11 (26.2) | 6 (21.4) | 0.65 | 0 (0.0) | 0 (0.0) | 2 (33.3) | 1 (14.3) |
| Clinical score | 4.5 (1.4) | 4.7 (1.3) | 4.7 (1.6) | 1.0 | 4.25 (0.5) | 3.5 (0.7) | 3.1 (0.7) | 4.1 (1.7) |
| Others clinical signs | | | | | | | | |
| Odynophagia | 12 (13.5) | 7 (16.6)) | 4 (14,3) | 0.53 | 1 (25) | 1 (1) | 0 (0) | 0 (0) |
| Digestives signs | 10 (11.2) | 5 (11.9) | 5 (17.8) | 0.52 | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Respiratory sign | 5 (5.6) | 4 (9.5) | 1 (3.6) | 0.33 | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Rhinitis | 15 (16.8) | 5 (11.9) | 9 (32.1) | 0.038 | 0 (0) | 0 (0) | 0 (0) | 1 (14.3) |
| Pharyngitis | 8 (9.0) | 2 (4.7) | 5 (17.8) | 0.085 | 0 (0) | 0 (0) | 0 (0) | 1 (14.3) |
| Encephalitis | 1 (1.1) | 0 (0) | 1 (3.5) | 0.40 | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Hospitalization | 16 (17.9) | 9 (21.4) | 3 (10.7) | 0.20 | 1 (25) | 1 (50) | 1 (16.6) | 1 (14.3) |
| Odynophagia | 9 | 5 | 2 | | 1 | 1 | 0 | 0 |
| Hyperthermia | 3 | 1 | 0 | | 0 | 0 | 1 | 1 |
| Neurological signs† | 1 | 1 | 1 | | 0 | 0 | 0 | 0 |
| Vomissements | 1 | 1 | 0 | | 0 | 0 | 0 | 0 |
| Skin severity | 1 | 1 | 0 | | 0 | 0 | 0 | 0 |

Data are mean (standard deviation) for age, fever and clinical score, discrete variable are expressed as count (%). Clinical score correspond to the mean number of anatonomical sites involved (mouth or peri-oral, hands, feet, buttock, trunk, legs, arms)

*Significant variation between CV6-A6 and CV-A16 groups were evaluated using analysis of variance for age, temperature, clinical score and $\chi^2$ test or Fisher's exact test for discrete variable (clinical characteristics).

†One child with febrile seizure and 1 with psychomotor retardation and aphasia regressive in 24 hours.




* The anatomical sites are hand, foot, mouth or perioral, buttock, trunk, legs, arms

**FIGURE 1.** Distribution of cases according to the number of anatomical sites involved.

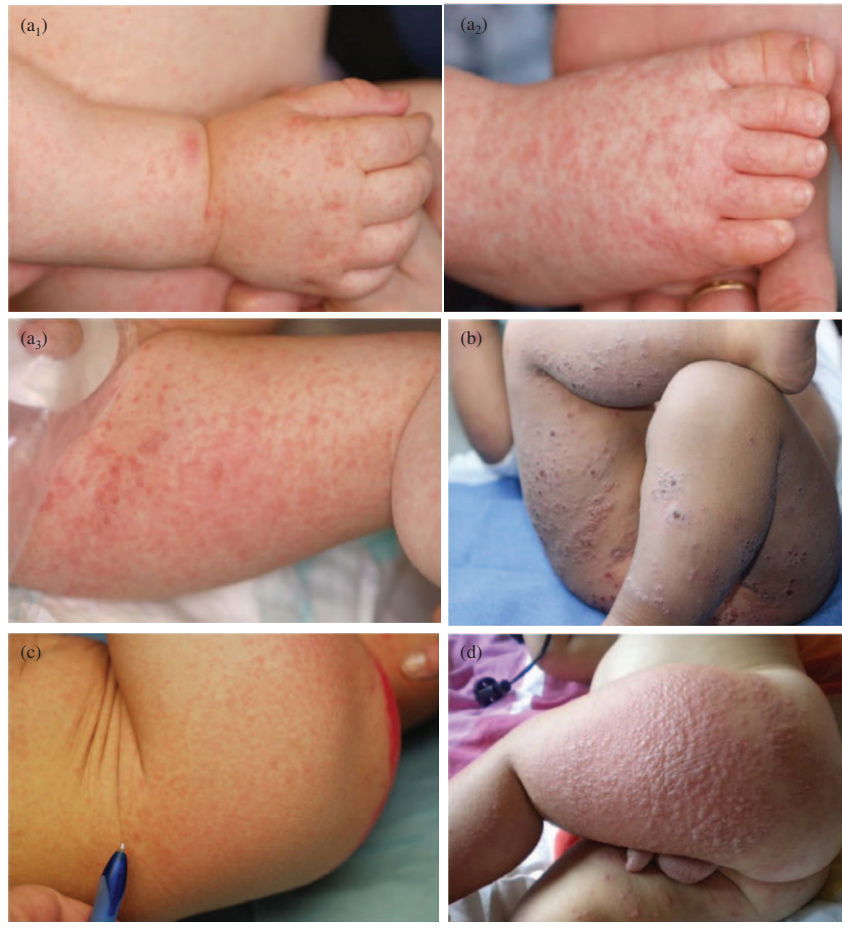



**FIGURE 2.** Clinical photographs of patients: A1–3) generalized HFMD related to CV-A16 in a 13-month-old boy; B) generalized HFMD related to CV-A6 in a 12-month-old boy; C) grouped vesicles in a 23-month-old boy with HFMD related to CV-A16 and D) grouped vesicles in an 18-year-old boy with HFMD related to CV-A6

Eighty-six children (96.6%) had vesicles and 34 (38.2%) had papules or superficial crusts. Thirty-one (34.8%) had both vesicles and crusts and none had purpuric petechial rash. Photographs of the dermatological lesions were taken and analyzed for 47 (52.8%) confirmed HFMD. The photographic analysis showed that vesicles were surrounded by erythema and between 1 and 5 mm in size. Vesicles were either isolated or grouped in large patches (Figs. 2 and 3). Eight patients (17%) had grouped vesicles. These grouped vesicles were related to eczema coxsackium in 2 patients. These patients had medical history of atopic dermatitis and the grouped vesicles were concentrated on atopic dermatitis bastion areas (Fig. 3B). The 6 others patients were not considered to have eczema coxsackium, because there was no atopic dermatitis and skin lesions were concentrated outside the classical atopic dermatitis bastion areas (Fig. 2A, C, D).

Nondermatological manifestations are summarized in Table 1. A total of 16 children (17.9%) were hospitalized. Ten were hospitalized because of low fluid intake associated with either odynophagia (n = 9) or vomiting (n = 1). Three were hospitalized due to poorly tolerated high fever and 1 because of extensive skin lesions. Two showed neurological signs: 1 child with febrile seizure and another with psychomotor retardation and aphasia which regressed within 24 hours. All children had favourable outcomes.

The comparison of the clinical characteristics of the patients did not show any significant difference between PCR-positive and PCR-negative patients.

## Genotypes

Genotyping was successful for 82 (92.1%) patients. Nine serotypes were identified (Fig. 4). CV-A6 and CV-A16 were identified in 42 (51.2%) and 28 (34.1 %) cases, respectively. The other EV identified were CV-A 10 (n = 4), EV-71 (n = 2), CV-A9 (n = 2), CV-A8 (n = 1), CV-B2 (n = 1), CV-B3 (n = 1) and E-9 (n = 1).

## Comparison Between Genotypes and Clinical Forms

Comparisons of clinical characteristics according to serotypes were analyzed for only CV-A6 and CV-A16 groups (Table 1). The mean number of anatomical sites involved was 4.7 for CV-A6 and CV-A16 infections ($P$ = 1; Table 1). The distribution of cases according to the number of anatomical sites involved and genotype is shown in Figure 1. The percentages of CV-A6- and CV-A16-related cases with 5 or more anatomical sites involved were 41.6% and 46.4%, respectively ($P$ = 0.49; Fig. 1). Peri-oral rash was more frequent in CV-A6 infections than in CV-A16 infections ($P < 0.001$).

Eczema coxsackium was related to CV-A6 (Fig. 2B) in 1 case but the genotype could not be determined for the other. The 6 other cases with grouped vesicles were related to CV-A6 (n = 4) and CV-A16 (n = 2) infections. The proportion of patients with grouped vesicles was 20.8% in CV-A6 and 15.4% CV-A16 infections ($P$ = 1.0).

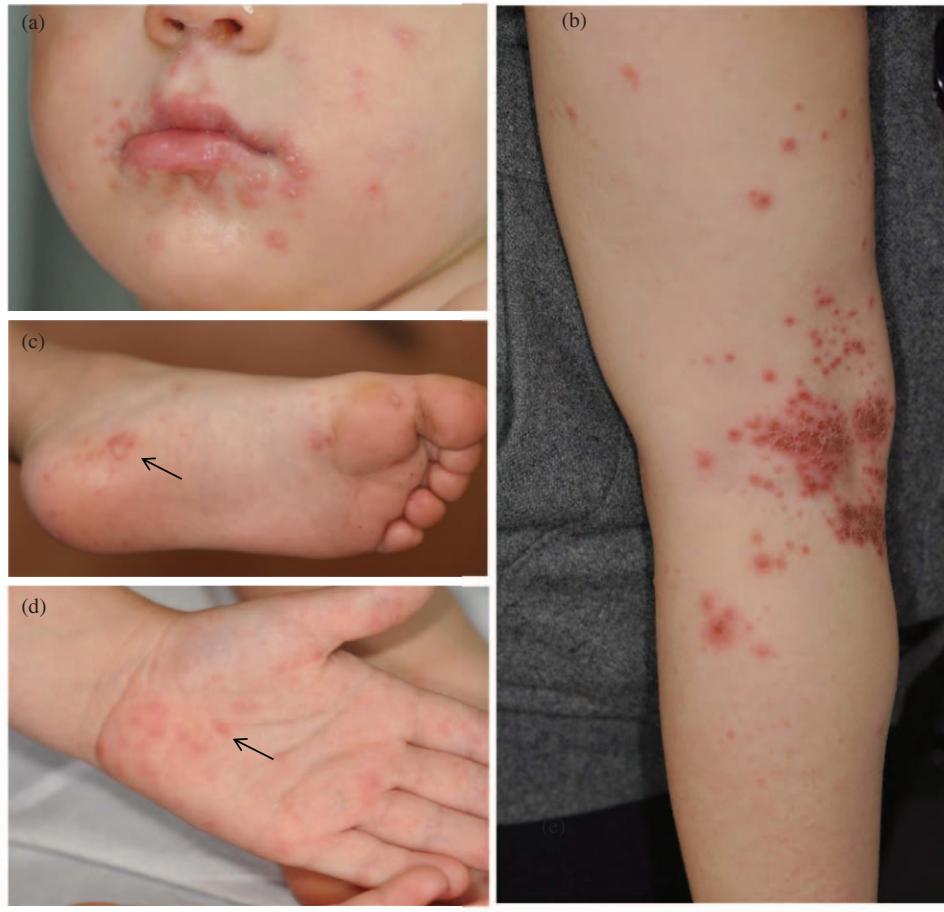



**FIGURE 3.** A) Peri-oral rash in an 18-month-old boy with CV-A6 HFMD; B) eczema coxsackium related to CV-A6 infection in a 28-month-old boy; C,D) plantar and palmar vesicles with pseudo-petechial lesions (arrow) related to CV-A16 (C) and CV-A6 (D) infections.

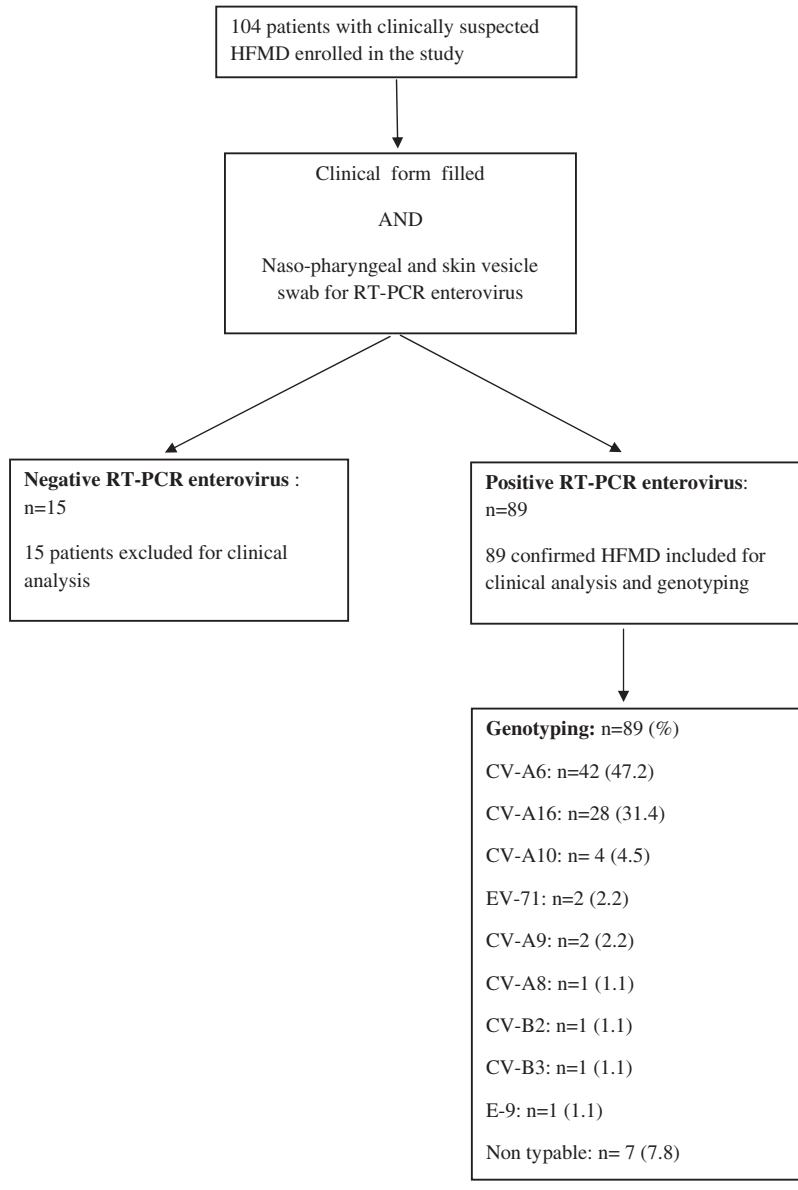



**FIGURE 4.** Inclusion criteria and serotypes identified by genotyping in confirmed HFMD cases.

## DISCUSSION

This study is based on solid prospective clinical and virological data, because all 89 diagnoses were confirmed virologically and 82 isolates were genotyped. This is the first long-term prospective dermatological study conducted that includes several outbreaks related to different serotypes. Most recent studies have been retrospective and conducted during an epidemic or with few cases confirmed by virological analysis.[8–12]

This study shows that HFMD is often presented as a diffuse vesicular rash: 37 children (41.5%) had lesions in at least 5 anatomical sites and were considered to have widespread exanthema. HFMD patients may also present only a few lesions, 12% of the patients had skin lesions on only 2 bastion areas (HFM). This study shows that HFMD may be characterized by a wide clinical spectrum ranging from localized vesicles to widespread vesicular exanthema. This result underlines that diffuse vesicular rash should not exclude a diagnosis of HFMD.

Widespread vesicular exanthema has recently been reported in an American retrospective study.[12] Such a generalized exanthema could be confused with other childhood vesicular exanthemas such as varicella. As with varicella, the elementary lesion is a vesicle followed later by a crust. More than one-third of the children in our study (35%) had both vesicles and crusts showing different stages in the evolution of lesions (Fig. 2B). However, we found some specific features of HFMD: first, the scalp was not involved and second, skin lesions were present in all bastion areas (HFM) or at least in 2 for 66% and 100%, respectively.

The elementary skin lesion in HFMD is usually a vesicle surrounded by erythema. However, in our study, atypical skin lesions were observed. Eight children (17%) had grouped vesicles leading to large erythematous patches of vesicles on the buttocks or thighs (Fig. 2A, C, D). This clinical characteristic has rarely been reported.[8,9,13] Grouped vesicles can also be observed in eczema coxsackium, but this diagnosis was ruled out because of the absence of atopic dermatitis and other acantholytic dermatoses.[12] Furthermore, in eczema coxsackium,

vesicles are concentrated on classical atopic dermatitis bastion areas (Fig. 3B). All our patients with large vesicular plaques or eczema coxsackium could have been confused with other conditions, mainly herpetic infections, but all HFMD patients had typical lesions also located over HFM. Petechial purpura has been reported in HFMD and could also lead to misdiagnosis. We did not observe any petechial purpura. Vesicles on the palms and soles can be deeper in the epidermis giving a clinical aspect of erythematous maculopapules or petechial purpura (Fig. 3C, D). It is important to distinguish these HFMD skin lesions from those of true petechial rash seen with other benign viral infections, such as parvovirus B19 infection.[15]

According to several retrospective studies conducted during recent CV-A6 outbreaks, HFMD related to this serotype may have a more severe or atypical rash.[8–13] However, in our study, such widespread vesicular rash was observed with both CV-A16 and CV-A6. It was not possible to distinguish between infections related to CV-A6, CV-A16 and other serotypes based on clinical severity assessment (Table 1, Fig. 1). Another atypical dermatological pattern concerned grouped vesicles (Fig. 2 A, C, D). This characteristic was found with both CV-A6 (20.8 %) and CV-A16 (15.4%). This clinical characteristic, described as vesicullobullous lesion, has been reported to be associated with CV-A6.[12] The only significant difference we found was the predominance of peri-oral rash with CV-A6 infection (CV-A6: 69.4%; CV-A16: 17.8%; $P < 0.001$). This was higher than that reported in 2 retrospective studies conducted in Taiwan (22%) and in the United States (41%).[8,9] HFMD related to EV-71 infection has been associated in Asia with a high rate of morbidity and mortality. All our cases had favourable outcomes. The 3 main serotypes, CV-A6, CV-A16 and CV-A10, isolated in our study confirm the circulation of different serotypes in Europe between 2008 and 2012 and might explain the absence of severe cases in our study.[16–19]

The main limitation of this study was recruitment that was based on a hospital network of mostly secondary or tertiary pediatric dermatological centers. This might have led to overestimation of the frequency of the generalized form of HFMD.

The dermatological signs of HFMD range from classical to generalized vesicular rash and may include atypical skin lesions. Generalized vesicular exanthema was observed with CV-A6 and CV-A16. Although peri-oral rash suggests CV-A6 infection, atypical dermatological lesions are not exclusive to this serotype.

## REFERENCES


1. Ho M, Chen ER, Hsu KH, *et al*. An epidemic of enterovirus 71 infection in Taiwan. Taiwan Enterovirus Epidemic Working Group. *N Engl J Med*. 1999;341:929–935.
2. Robinson CR, Doane FW, Rhodes AJ. Report of an outbreak of febrile illness with pharyngeal lesions and exanthem: Toronto, summer 1957; isolation of group A Coxsackie virus. *Can Med Assoc J*. 1958;79: 615–621.
3. Bendig JW, Fleming DM. Epidemiological, virological, and clinical features of an epidemic of hand, foot, and mouth disease in England and Wales. *Commun Dis Rep CDR Rev*. 1996;6:R81–R86.
4. Chatproedprai S, Theanboonlers A, Korkong S, *et al*. Clinical and molecular characterization of hand-foot-and-mouth disease in Thailand, 2008-2009. *Jpn J Infect Dis*. 2010;63:229–233.
5. Clementz GC, Mancini AJ. Nail matrix arrest following hand-foot-mouth disease: a report of five children. *Pediatr Dermatol*. 2000;17:7–11.
6. Osterback R, Vuorinen T, Linna M, et al. Coxsackievirus A6 and hand, foot, and mouth disease, Finland. *Emerg Infect Dis*. 2009;15:1485–1488.
7. Davia JL, Bel PH, Ninet VZ, et al. Onychomadesis outbreak in Valencia, Spain associated with hand, foot, and mouth disease caused by enteroviruses. *Pediatr Dermatol*. 2011;28:1–5.
8. Wei SH, Huang YP, Liu MC, et al. An outbreak of coxsackievirus A6 hand, foot, and mouth disease associated with onychomadesis in Taiwan, 2010. *BMC Infect Dis*. 2011;11:346.
9. Centers for Disease Control and Prevention (CDC). Notes from the field: severe hand, foot, and mouth disease associated with coxsackievirus A6 - Alabama, Connecticut, California, and Nevada, November 2011-February 2012. *MMWR Morb Mortal Wkly Rep*. 2012;61:213–214.
10. Flett K, Youngster I, Huang J, et al. Hand, foot, and mouth disease caused by coxsackievirus a6. *Emerg Infect Dis*. 2012;18:1702–1704.
11. Chen YJ, Chang SC, Tsao KC, et al. Comparative genomic analysis of coxsackievirus A6 strains of different clinical disease entities. *PLoS One*. 2012;7:e52432.
12. Mathes EF, Oza V, Frieden IJ, et al. "Eczema coxsackium" and unusual cutaneous findings in an enterovirus outbreak. *Pediatrics*. 2013;132:e149–e157.
13. Huang WC, Huang LM, Lu CY, et al. Atypical hand-foot-mouth disease in children: a hospital-based prospective cohort study. *Virol J*. 2013;10:209.
14. Nix WA, Oberste MS, Pallansch MA. Sensitive, seminested PCR amplification of VP1 sequences for direct identification of all enterovirus serotypes from original clinical specimens. *J Clin Microbiol*. 2006;44: 2698–2704.
15. Edmonson MB, Riedesel EL, Williams GP, et al. Generalized petechial rashes in children during a parvovirus B19 outbreak. *Pediatrics*. 2010;125:e787–e792.
16. Badran SA, Midgley S, Andersen P, et al. Clinical and virological features of enterovirus 71 infections in Denmark, 2005 to 2008. *Scand J Infect Dis*. 2011;43:642–648.
17. Mirand A, Henquell C, Archimbaud C et al. Outbreak of hand, foot and mouth disease/herpangina associated with coxsackievirus A6 and A10 infections in 2010, France: a large citywide, prospective observational study. *Clin Microbiol Infect*. 2012;18:E110-8
18. Osterback R, Vuorinen T, Linna M, et al. Coxsackievirus A6 and hand, foot, and mouth disease, Finland. *Emerg Infect Dis*. 2009;15:1485–1488.
19. Blomqvist S, Klemola P, Kaijalainen S, et al. Co-circulation of coxsackieviruses A6 and A10 in hand, foot and mouth disease outbreak in Finland. *J Clin Virol*. 2010;48:49–54.

## APPENDIX

**APPENDIX 1.** English translation of the form used to record clinical findings

# Hand foot Mouth disease : observational study

Patient n° Date :…../…../……

Date of birth : …../…../…… Male ☐ Female ☐

### Inclusion criterion

**Clinical diagnosis of hand foot mouth disease** **YES** ☐ **NO** ☐

**AND**

**Virological swab** **YES** ☐ **NO** ☐

### Clinical characteristics

**Body temperature :**……..° Fatigue : YES ☐ NO ☐

Dermatological feature

| | Vesicles | Papules / crusts | |
|---|---|---|---|
| Mouth | ☐ | ☐ | |
| Hand | ☐ | ☐ | |
| Foot | ☐ | ☐ | |
| Perioral | ☐ | ☐ | |
| Buttock | ☐ | ☐ | |
| Others localization | ☐ | ☐ | Please specify :…… |

Others dermatological diseases:……

**Photos** Yes ☐ NO ☐

Extra dermatological symptoms

**Complications : YES** ☐ **NO** ☐

**Hospitalization : YES** ☐ NO ☐ If yes, why ::……

Neurological signs

Seizure ☐
Hypotonia ☐
Meningeal syndrome ☐
Encephalitis ☐
Paralysis ☐
Polyradiculopathy ☐
Ataxia ☐

Respiratory signs

Rhinitis ☐
Pharyngitis ☐
Bronchiolitis ☐
Pneumonia ☐

Cardiovascular signs

Myocarditis ☐
Pericarditis ☐
Shock syndrome ☐

Digestive signs

Vomiting ☐
Diarrhea ☐
Abdominal pain ☐

Ocular signs

Conjunctivitis ☐
Hemorrhagic conjunctivitis ☐

### Epidemiological characteristics

Recent travel : Yes ☐ No ☐ If yes, date and country……

Other cases: Yes ☐ No ☐

In family : Yes ☐ No ☐ Number of cases……

In school / day care Yes ☐ No ☐ Number of cases:……