CLINICAL AND LABORATORY INVESTIGATION

Onychomadesis Outbreak in Valencia, Spain Associated with Hand, Foot, and Mouth Disease Caused by Enteroviruses

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Abstract: This report evaluates the June 2008 onychomadesis outbreak in Valencia, Spain. The study sample consisted of 221 onychomadesis cases and 77 nonaffected individuals who lived close to those affected. We collected data on dietary variables, hygiene products, and individual pathological histories. Feces and blood specimens were collected from 44 cases and 24 controls to evaluate exposure to infectious agents. Pathological background data revealed a high frequency (61%) of hand, foot, and mouth disease among the onychomadesis cases. Coxsackievirus A10 was the most commonly detected enterovirus in both case and control groups (49%). Other enteroviruses such as coxsackieviruses A5, A6, A16, B1, and B3; echoviruses 3, 4, and 9; and enterovirus 71 were present in low frequencies in the case and control groups (3–9%). The 2008 onychomadesis outbreak in the metropolitan area of Valencia was associated with an outbreak of hand, foot, and mouth disease primarily caused by coxsackievirus A10.

Nail matrix arrest has been associated with some systemic illnesses caused by infections and drug exposure, although many cases are idiopathic. A wide range of nail dystrophies may result, from transverse ridging of the nail plate (Beau's line) to complete nail shedding from the proximal portion without pain or inflammation (onychomadesis) (1,2). Hand, foot, and mouth disease (HFMD) has been reported as a possible cause of onychomadesis (3,4). HFMD is a common childhood illness characterized by fever and vesicular eruptions on the hands, feet, and mouth. Complications are rare, but pneumonia, meningitis, rhabdomyolisis, or encephalitis may occur. It is associated with different strains of the coxsackievirus (CV), most commonly A16 (5,6), but also other A and B types (7–12) and enterovirus 71 (13).

This article reports on an onychomadesis outbreak in Valencia, Spain. Although this outbreak has been previously associated with HFMD (3,4), we publish in this study the epidemiologic and etiologic results from an expanded case sample (14).

PATIENTS AND METHODS

We identified 311 onychomadesis cases attended in different health centers and hospitals of Valencia from the spring of 2008 and 83 nonaffected individuals who lived close to those affected. The sample population resided in the metropolitan area of Valencia. Of the 311 cases, 221 (71%) were well-documented and formed our case group; 77 of the 83 nonaffected individuals (93%) agreed to participate in the study as the control group. In the case group, 164 individuals were of school or preschool age and 57 cases were related to them. The seven adults in the case group did not have professional relationships with educational centers. We defined onychomadesis cases (Fig. 1) as loss of two or more nails from fingers or toes and no previous traumatic or systemic disease. Control individuals did not have onychomadesis but shared a house or school center with at least one onychomadesis case. Diagnoses for 20% of the cases in our sample had been provided by dermatologists, 53% by pediatricians and the remainder by other specialists.

We evaluated eating habits (sweets, water, etc.), hygiene products, and pathologic background for all case and control individuals by an exhaustive questionnaire that was filled in by children's parents. We also tested local animals for fungi and parasites.

Feces and blood specimens were collected from 44 cases and 24 controls to evaluate their exposure to enteroviruses (other cases and controls did not agree to provide blood and feces specimens). We also conducted molecular analysis of samples from the patients' feces, including polymerase chain reaction (PCR) amplification. The detected viruses were sequenced and typed.

Contingency tests (2 × 2 tables) were performed to establish a relationship between HFMD and onychomadesis.

RESULTS

A high percentage (96%) of onychomadesis cases were in children younger than 6 years of age, with similar numbers of males and females affected. The cases were distributed between February 1 and July 1, 2008. The timing of the outbreak suggested the existence of five progressively more intensive and widely distributed epidemic waves, reinforcing the hypothesis that onychomadesis was associated with person-to-person transmission of an infectious disease (Fig. 2).

The case and control groups showed no significant differences in eating habits (including consumption of sugary foods) or exposure to animals, hygiene products and other elements.

The pathologic background data revealed a high frequency (61%) of HFMD among onychomadesis cases (Table 1). The odds ratio (OR) produced by contingency
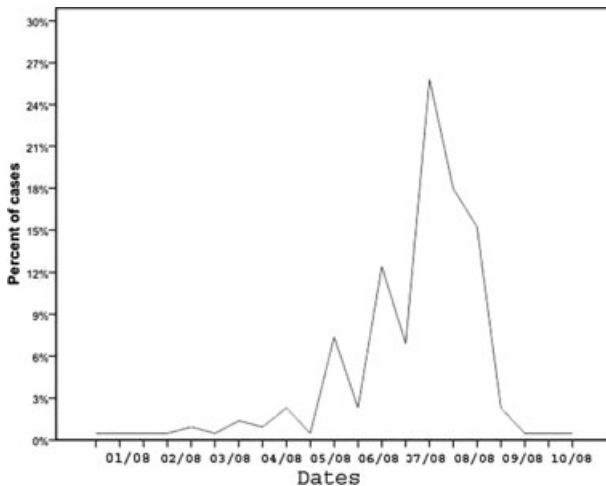

Figure 1. Onychomadesis cases.

Figure 2. Onychomadesis cases in Valencia, Spain, 2008.

TABLE 1. *Previous Diagnosis or Reason for Attending to Medical Consultation. Period of 15 to 60 Days Previous to Onychomadesis (221 Cases and 77 Controls)*

	Case	Control	Total
HFMD+	131	10	141
HFMD−	61	63	124
Total	192	73	265
Pearson's chi-square	63.169		
p	0.1001		
OR	13.52		
CI 95%	6.49 to 28.16		

analysis was 13.53 (confidence interval: 95%; range: 6.5–28.16). We selected children under 6 years of age (95% cases and controls) (Table 2).

The median latency period between HFMD and onychomadesis was 39 days (SD: 28, 29 days; percentile 25%: 24; percentile 75%: 55).

Immunoglobulin M (IGM) enteroviruses were detected in 15% of the total sample, and immunoglobulin G (IGG) enteroviruses were detected in 59% of the sample. No significant differences were found between case and control groups. IGG serology revealed a significant relationship with HFMD antecedents. This relationship was not present with the IGM enteroviruses.

Enteroviruses were detected in 35 fecal samples (26 cases [66%] and 9 controls [37.5%]). The most common enterovirus in both case and control groups was CVA10 (49%; Fig. 3). Our analysis also detected low frequencies (3–9%) of the following enteroviruses in both groups: CVA5, CVA6, CVA16, CVB1, and CVB3; echoviruses 3 (E3), 4 (E4), and 9 (E9); and enterovirus 71 (EV71).

DISCUSSION

Hand, foot, and mouth disease has been previously associated with Beau's lines and onychomadesis (3,4). Clementz and Mancini (3) reported on five children from the Chicago metropolitan area, aged 22 months to 4 years, who presented with Beau's lines or onychomadesis 3 to 8 weeks after physician-diagnosed HFMD. A similar latency period was observed in our study. Clementz et al suggested that all patients were infected with the same viral strain, and that the cases thus represented an "epidemic" of HFMD caused by a virus capable of inducing nail matrix arrest. However, the authors did not identify the responsible virus. Bernier et al (4) reported four isolated cases of onychomadesis following HFMD from France and Belgium, suggesting that more than one viral strain may have been implicated in the nail matrix arrest. Our study supports this suggestion, because we verified multiple strains of enteroviruses that could cause onychomadesis. Our study presents the first identification of the etiological agents (enteroviruses) responsible for the 2008 Valencia outbreak of onychomadesis following HFMD.

Conditions reported in association with Beau's lines include severe systemic diseases, nutritional deficiencies,

TABLE 2. *Relationship Between Onychomadesis and HFMD for Children Under 6 yrs of Age*

| Pathology	Case	Percent (%)	Control	Percent (%)	Total
Hand-foot-and-mouth disease	134	60.63	10	12.99	144
Not recorded	60	27.15	59	76.62	119
Tonsilitis	32	14.48	6	7.79	38
Uncertain FHM disease	18	8.14	2	2.60	20
Chickenpox	14	6.33	1	1.30	15
Unspecified fever	15	6.79	6	7.79	21
Respiratory acute infection	12	5.42	2	2.60	14
Otitis	10	4.52	1	1.30	11
Diarrhea digestive syndrome	4	1.81	1	1.30	5
Mononucleosis	3	1.36		0.00	3
Urine infection	2	0.90		0.00	2
Conjunctivitis	1	0.45	1	1.30	2
Others	8	3.61		0.00	8
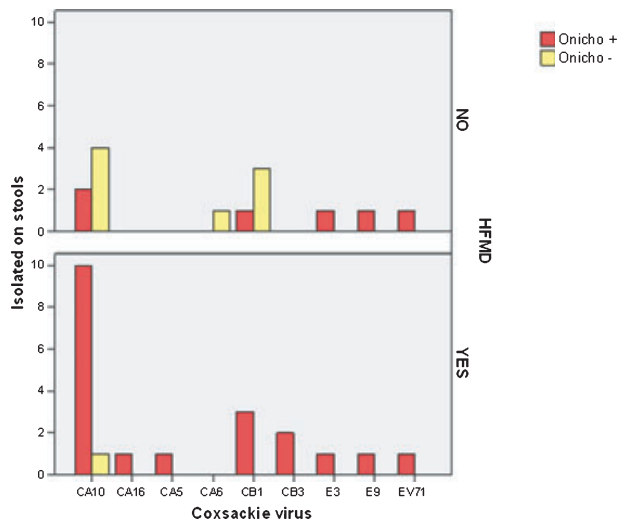
Figure 3. Enterovirus in feces. Distribution by onychomadesis and hand, foot, and mouth disease (HFMD).

trauma, periungueal dermatitis, chemotherapy administration, fever, dysmenorrhea, drug ingestion, myocardial infection, renal failure, reflex sympathetic dystrophy, and infection (15–17). Onychomadesis shares several proposed etiologies with Beau's lines. None of these features was present in our outbreak. In our study, onychomadesis was caused by a benign viral infection rather than by severe systemic disease, toxic or pharmacological therapy. We observed no relationship between onychomadesis and the severity of the preceding HFMD in our patients. The nail matrix arrest mechanism is unclear in our patients, although Osterback et al (8) detected CVA6 in shed nail fragments of a patient who suffered onychomadesis following HFMD. The authors suggested that virus replication damaged nail matrix and resulted in a temporary nail dystrophy. In all of our cases, nail changes were temporary with spontaneous normal regrowth, because the nail basement remains intact in onychomadesis.

Enteroviruses are the most common viruses worldwide (18). HFMD is a viral infection associated mainly with EV71 and CVA16. In our study the outbreak of HFMD was caused by CVA10. This finding contradicts the conclusions reached by Spanish virological surveillance over the last decade, which has identified CVA16 as the main virus implicated in HFMD outbreaks (19). Sporadic cases associated with CVA4, CVA7, CVA9, CVA10, CVB1, CVB3, and CVB5 have also been reported.

Enteroviruses were detected in only 35 of the 68 fecal samples analyzed in this study. The time elapsed between sample collection and HFMD symptoms, related to the latency period of onychomadesis, likely reduced the number of viruses we found. Detection of CV10 in controls may correspond to asymptomatic infections.

In conclusion, the 2008 onychomadesis outbreak in the metropolitan area of Valencia, Spain was primarily associated with an outbreak of HFMD caused by CVA10. Our study reinforces existing evidence for the relationship between previous HFMD and onychomadesis. The strong association between the two conditions, their temporal relationship and the absence of intermediate pathologies confirm the causal relationship. This association may suggest changes in the molecular and physiologic activity of the enterovirus species that provoked benign dermatological manifestations. Dermatologists, pediatricians, and other specialists should find this knowledge useful in providing diagnoses and discussing the condition with patients and their families.

In our review of the medical literature, we have not found an ongoing epidemic outbreak of onychomadesis anywhere else in the world. The onychomadesis outbreak has not resurfaced in Spain during 2009, for unknown reasons.

REFERENCES

1. Daniel CR, Scher RK. Nail changes secondary to systemic drugs or ingestants. J Am Acad Dermatol 1984;10: 250–258.
2. Bodman MA. Miscellaneous nail presentations. Clin Pediatr Med Surg 1995;12:327–347.
3. Clementz GC, Mancini AJ. Nail matrix arrest following hand-foot-mouth disease: a report of five children. Pediatric Dermatol 2000;17:7–11.
4. Bernier V, Labreze C, Bury F et al. Nail matrix arrest in the course of hand, foot and mouth disease. Eur J Pediatr 2001;160:649–651.
5. Cherry JD, Jahn CL. Hand, foot and mouth syndrome. Report of six cases due to coxsackievirus, group A, type 16. Pediatrics 1966;37:637–645.
6. Bending WA, Fleming DM. Epidemiological, virological and clinical features of an epidemic of hand, food and mouth disease in England and Wales. CDR Rev 1996;6:R81–R86.
7. Flewett TH, Warrin RP, Clarke SKR. Hand, foot and mouth disease associated with Coxsackie A5 virus. J Clin Pathol 1963;16:53–55.
8. Osterback R, Vuorinen T, Linna M et al. Coksackie virus A6 and hand, foot and mouth disease, Finland. Emerg Infect Dis 2009;15:1485–1488.
9. Duff MF. Hand-foot-and-mouth syndrome in humans. Coxsackievirus A10 infections. New Zealand. Br Med J 1968;2:661–664.
10. Cherry JD. Enteroviruses: polioviruses (poliomyelitis), coxsackieviruses, echoviruses and enteroviruses. In: Feigin RD, Cherry JD, eds. Textbook of pediatric infectious diseases, 3rd edn. Philadelphia: WB Saunders, 1993: 1705–1753.

11. Lindenbaum JE, Van Dyck PC, Allen RG. Hand, foot and mouth disease associated with coksackievirus group B. Scand J Infect Dis 1975;7:161–163.

12. Moreira RC, Castrignano SB, Carmona RC et al. An exanthematic disease epidemic associated with coxsackievirus B3 infection in a day care center. Rev Inst Med Trop Sao Paulo 1995;37:235–238.

13. Ishimaru Y, Nakano S, Yamaoka K et al. Outbreaks of hand, foot, and mouth disease by enterovirus 71. Arch Dis Child 1980;55:583–588.

14. Salazar A, Febrer I, Guiral S et al. Onychomadesis outbreak in Valencia, Spain, June 2008. Euro Surveill 2008;13:pii: 18917.

15. Colvett KL, Patel D, Smith JK. Multiple Beau's lines in a patient with fever of unknown origin. South Med J 1993;86:1424–1426.

16. De Berker D. What do Beau's lines mean? Int J Dermatol 1994;33:545–546.

17. Ben-Dayan D, Mittelman M, Floru S et al. Transverse nail ridgings (Beau's lines) induced by chemotherapy. Acta Haematol 1994;91:89–90.

18. CDC-Atlanta. Enterovirus surveillance—United States, 1970–2005. MMWR Surveill Summ 2006;55:1–20.

19. Trallero G, Casas I, Tenorio A et al. Enteroviruses in Spain: virological and epidemiological studies over 10 years (1988–97). Epidemiol Infect 2000;124:497–506.