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Belsy Acosta, Alexander Piñón, Odalys Valdés, Clara Savón, Amely Arencibía, Elías Guilarte, Gonzalez Grehete, Suset Oropesa, Gonzalez Guelsys, Bárbara Hernández, Angel Goyenechea, Mayra Muné, Vivian Kouri, María G. Guzmán, and Alina Llop

Author affiliation: Instituto Pedro Kourí, Havana, Cuba

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Address for correspondence: Belsy Acosta, Instituto Pedro Kourí, Autopista Novia del Mediodía Km 6½, La Lisa, CP 17 100, Havana, Cuba; email: betsy@ipk.sld.cu

Letters

Letters commenting on recent articles as well as letters reporting cases, outbreaks, or original research are welcome. Letters commenting on articles should contain no more than 300 words and 5 references; they are more likely to be published if submitted within 4 weeks of the original article's publication. Letters reporting cases, outbreaks, or original research should contain no more than 800 words and 10 references. They may have 1 Figure or Table and should not be divided into sections. All letters should contain material not previously published and include a word count.

Hand, Foot, and Mouth Disease Caused by Coxsackievirus A6, Japan, 2011

To the Editor: Coxsackievirus A6 (CVA6) belongs to human enterovirus species A of the genus *Enterovirus*. According to a Japanese Infectious Agents Surveillance Report, this virus is one of the major causes of herpangina, an acute febrile disease characterized by vesicles, ulcers, and redness around the uvula, which occurs mainly in young children and infants. (*1*).

In June 2011, a sudden increase in cases of hand, foot, and mouth disease (HFMD) at pediatric sentinel sites (≈3,000 pediatric hospitals and clinics) was reported to the National Epidemiologic Surveillance of Infectious Diseases System in Japan. Compared with past numbers of cases over 30 years of surveillance, the number of cases of HFMD per sentinel site peaked in week 28 (July) of 2011 (10.97 cases per sentinel), particularly in western Japan (*2*). According to the Infectious Agents Surveillance Report (as of September, 18, 2011), CVA6 was detected in 709 HFMD cases and 156 herpangina cases throughout Japan (*1*).

Clinical samples (throat swab specimens and feces) obtained from sentinel sites in Shimane, Hyogo, Hiroshima, and Shizuoka, Japan, were screened for enteroviruses by using an enterovirus-specific reverse transcription PCR and sequence analysis of the partial viral protein (VP)4/VP2 or VP1 region (*3*). Among 93 clinical samples from 108 HFMD case-patients, we identified 74 case-patients as CVA6 positive by sequence analysis.

On the basis of sequence analysis of the entire VP1 region (GenBank accession nos. AB649286–AB649291), the consensus sequence

had 82.3%–82.5% nt identity (94.8%–95.4% aa identity) with the prototype CVA6 Gdula strain (GenBank accession no. AY421764). CVA6 was not isolated from clinical samples in a cell culture system. Therefore, most CVA6 strains were identified by molecular detection directly from clinical samples and sequence analysis. Some CVA6 strains were grown and isolated in suckling mice; these strains were antigenically identified as CVA6 by a neutralization test with specific antiserum against CVA6 (*4*).

In Japan, HFMD and herpangina are classified as category V infectious diseases. On the basis of clinical diagnosis, suspected infections were reported by pediatric sentinel sites on a weekly basis to the Infectious Disease Surveillance Center of the National Institute of Infectious Diseases (Tokyo, Japan). Typical clinical signs and symptoms of HFMD cases caused by CVA6 were fever, mild vesicles in oral mucosa, and skin blisters on hands, arms, feet, legs, buttocks, and nail matrixes (Figure). Some patients with HFMD had onychomadesis (periodic shedding of the nails) 1–2 months after onset of HFMD. Most cases of HFMD were self-limited. However, additional follow-up may be necessary for patients with onychomadesis who are treated at dermatology clinics.

As in other countries in the Asia–Pacific region, major causes of HFMD in Japan were CVA16 and enterovirus 71. In 2010, enterovirus 71 was identified as a major cause of HFMD (*1*). In contrast, CVA6 was consistently associated with herpangina, as were CVA2, CVA4, CVA5, and CVA10, but CVA6 was occasionally detected in HFMD case-patients. CVA6 was the major cause of herpangina in 2007, but an increase in the detection rate of CVA6 in HFMD case-patients was reported in Japan in 2009 (*1*).

HFMD outbreaks caused by CVA6 were reported in Singapore, Finland, and Taiwan in 2007–2009 (*5*–*8*). Recent HFMD outbreaks in Finland and Spain were associated with cases of onychomadesis 1–2 months after onset of HFMD (*6*,*8*,*9*). In Japan, cases of onychomadesis after onset of HFMD were reported in 2009 (*10*). Therefore, changes in clinical outcomes of CVA6-associated diseases should be investigated.

Although most HFMD cases caused by CVA6 in Japan were mild, CVA6 was also detected in other clinical samples, including cerebrospinal fluid from a patient with acute encephalitis in Hiroshima, which reaffirmed possible additional clinical manifestations during an HFMD outbreak caused by CVA6. Careful surveillance of disease and infectious agent activities are crucial in monitoring CVA6-associated HFMD, onychomadesis, and neurologic diseases. Nucleotide identity between CVA6 strains in Finland (2008) (*7*) and Japan (2011) was ≈95% in the partial VP1 region. More detailed genetic, phenotypic, and epidemiologic analyses of CVA6 are needed to determine the role of CVA6 in HFMD outbreaks with or without onychomadesis.

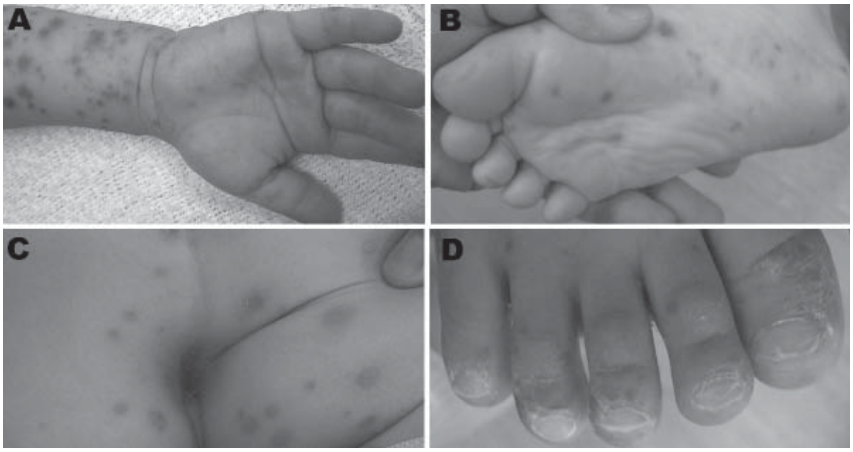

Figure. Typical clinical manifestations of hand, foot, and mouth disease associated with coxsackievirus CVA6 in Shizuoka, Japan, June–July, 2011. A) Hand and arm of a 2.5-year-old boy; B) foot and C) buttocks of a 6-year-old boy; D) nail matrix of a 20-month-old boy. A color version of this figure is available online (wwwnc.cdc.gov/EID/article/18/2/11-1147-F1.htm).

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Author affiliations: National Institute of Infectious Diseases, Tokyo, Japan (T. Fujimoto, K. Yamashita, N. Hanaoka, N. Okabe, H. Yoshida, Y. Yasui, H. Shimizu); Shimane Prefectural Institute of Public Health and Environmental Science, Shimane, Japan (S. Iizuka); Hyogo Prefectural Institute of Public Health and

Consumer Sciences, Hyogo, Japan (M. Enomoto); Hiroshima City Institute of Public Health, Hiroshima, Japan (K. Abe, Y. Fujii, H. Tanaka, M. Yamamoto); and Kobayashi Pediatric Clinic, Shizuoka, Japan (M. Kobayashi)

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Address for correspondence: Hiroyuki Shimizu, Department of Virology II, National Institute of Infectious Diseases, Gakuen 4-7-1, Musashimurayama-shi, Tokyo 208-0011, Japan; email: hshimizu@nih.go.jp

Human and Porcine Hepatitis E Viruses, Southeastern Bolivia

To the Editor: Hepatitis E virus (HEV) genotypes 3 and 4 are considered to be primarily zoonotic (*1*). However, recent data indicate that both genotypes can be transmitted among humans through other routes (*2*,*3*). Observations of genetic distinctiveness between swine and human HEV strains circulating within the same region argue against exclusivity of zoonotic transmission (*4*). A recent report presented a remarkable example of such distinction between genotype 3 isolates in rural communities in southeastern Bolivia (*5*).

We examined HEV sequences obtained in that study to show the independent genetic origin of swine and human variants. Findings suggest disjunction between human and swine HEV strains in this epidemiologic setting, despite the potential for extensive cross-species exposure.

Using reference sequences from Lu et al. (*6*), we conducted subtype analysis of HEV open reading frame 2 sequences at nucleotide positions 826–1173 (GenBank accession no. AF060668) from isolates from 2 rural communities in southeastern Bolivia (*5*). Analysis showed that swine sequences belonged to subtype 3i and that the human sequences belonged to 3e.

We collected all available GenBank genotype 3 sequences covering this genomic region for which the dates of collection were documented. Sequences were used to estimate the time from the most recent common ancestor (tMRCA) by using BEAST version 1.6.1 (*7*). Estimated tMRCA for GenBank sequences was longer than for sequences from Bolivia alone (Table) or for all genotype 3 sequences together (Table).

To reduce the effect of close relatedness among human or swine HEV sequences from Bolivia on the tMRCA estimate, we used only 1 representative sequence per species from each community in the final analysis. This analysis identified an estimated tMRCA similar to that seen for GenBank sequences alone (Table, model F vs. model D). This estimate indicates that human and swine HEV isolates from southeastern Bolivia last shared a common ancestor ≈275 years ago (Table, model F). Thus, swine HEV strains from both rural communities belonged to subtype 3i, and the human HEV strains identified from the community of Bartolo, Bolivia, belonged to subtype 3e and shared an ancestor with swine strains almost 3 centuries ago.

This finding is surprising because the community of Bartolo has several potential risk factors for zoonotic transmission of HEV. There are ≈200 humans and ≈70 swine in Bartolo (*8*). Residents are mainly native Quechua and Guarani with some of mixed Spanish ancestry who subsist at a low socioeconomic level. Their main livelihood activities are agriculture and breeding of animals. Free-range pig farms are family owned. Because of its impoverished state, the community has no running water, and few houses have toilets. No facilities are suitable for safely slaughtering