New Introductions of Enterovirus 71 Subgenogroup C4 Strains, France, 2012

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In France during 2012, human enterovirus 71 (EV-A71) subgenogroup C4 strains were detected in 4 children hospitalized for neonatal fever or meningitis. Phylogenetic analysis showed novel and independent EV-A71 introductions, presumably from China, and suggested circulation of C4 strains throughout France. This observation emphasizes the need for monitoring EV-A71 infections in Europe.

Human enterovirus 71 (EV-A71) is a member of the enterovirus species A in the family Picornaviridae, genus Enterovirus. On the basis of the 1D gene sequences encoding the VP1 capsid protein (1DVP1), EV-A71 has been classified into 3 genogroups (A–C) and 12 subgenogroups (A, B0–B5, C1–C5) (1); in addition, 3 new genogroups (D–F) were recently identified (2–4). In children, EV-A71 mainly causes asymptomatic or benign infections, such as neonatal fever and hand-foot and mouth disease (HFMD); less frequently, EV-A71 causes neurologic complications, such as encephalitis and poliomyelitis-like paralysis (1).

In the Asia–Pacific region, EV-A71 has emerged as a major public health concern over the past 15 years. Large outbreaks have been reported, associated with the emergence of new genogroups and subgenogroups, high rates of illness, and fatal cases of encephalitis (1,5). The largest epidemic expansion of EV-A71 occurred in China, mainly caused by EV-A71 subgenogroup C4 (EV-A71 C4) strains (5,6). By contrast, epidemic activity is low in Europe, where only 4 outbreaks of EV-A71 infection have been reported over the past 40 years: Bulgaria (1975), Hungary (1978), and the Netherlands (1986, 2007) (5,7). Most of the cases of EV-A71 infection reported since 1986 have been caused by subgenogroup C1 and C2 strains (7–9). In 2004, EV-A71 C4 strains were rarely detected in France, Germany, and Austria (8–11), and no other EV-A71 C4 cases were reported in Europe until 2012, when we detected C4 strains in 4 hospitalized patients, suggesting that dissemination of the C4 strains was restricted during 2004–2011. We describe the clinical cases caused by the EV-A71 C4 strains detected in 2012 and address the origin of these newly detected viruses.

The Study

In France, EV infections diagnosed in hospital settings have been voluntarily reported to the National Institute for Public Health by a network of hospital laboratories since 2000 (9). In 2012, a total of 2,088 EV infections were reported by the laboratory network. In addition, in 2010, a total of 158 community cases of HFMD and herpangina were reported through a sentinel surveillance system implemented in Clermont-Ferrand, France (12). As part of the national surveillance, 1,249 EV strains were analyzed by 6 laboratories in the EV network (including the 2 National Enterovirus Reference Center laboratories in Lyon and Clermont-Ferrand). Of the 1,249 EV strains, 1,105 (88.5%) were successfully genotyped. Most of the genotyped strains were detected in cerebrospinal fluid (CSF) samples from patients with neonatal fever, meningitis, or meningoencephalitis or in samples from patients with HFMD or herpangina. Of the 1,105 genotyped EV strains, 16 (1.4%) were EV-A71 strains. Among these 16 cases of EV-A71 infection, a fatal case of rhombencephalitis was diagnosed in an adult who had been treated with rituximab (13). On the basis of the complete 1D gene sequences encoding the VP1 capsid protein (1DVP1), 12 of the 16 EV-A71 strains were assigned to subgenogroup C2, and 4 were assigned to subgenogroup C4.

We conducted a retrospective review of medical records for the 4 patients with EV-A71 C4 infection to document the patients’ ages at diagnosis, clinical symptoms, length of hospitalization, and laboratory findings. The EV-A71 C4 infections were detected throughout the year in 3 regions (Brittany, Ile de France, and Provence-Alpes-Côte d’Azur). Of the 4 patients, 3 (6, 17, and 21 days of age) had neonatal fever when medical care was sought, and 1 patient (4 years of age) had meningitis (Table). The 21-day-old infant had persisting irritability and was hospitalized for 6 days. No severe neurologic complications were observed, and all 4 children had a favorable outcome. Bacterial culture results for CSF, blood, and urine samples from all 4

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children were negative, and molecular detection results for herpes simplex virus types 1 and 2 and varicella-zoster virus in CSF were also negative. For the 3 children with neonatal fever, reverse transcription PCR was positive for EV-A71 in CSF specimens. For the child with meningitis, reverse transcription PCR was positive for herpes simplex virus types 1 and 2 and varicella-zoster virus in CSF. In addition, for patients 1 and 4, molecular testing results were also negative for the detection of human herpesvirus type 6, cytomegalovirus, and Epstein-Barr virus. Results were also negative for CSF bacterial cultures. CSF, cerebrospinal fluid sample; Cc, cycle threshold; NA, not available; Neg, negative NP, nasopharyngeal sample; Pos, positive; RT-PCR, reverse transcription PCR.

†Nantes (47°13′N; 1°33′W; Brittany); Versailles (48°48′N; 2°08′E; Ile de France); Grasse (43°40′N; 6°55′E; Ile de France); Rennes (48°06′N; 1°40′W; Brittany).

‡The upper Ct for positivity for each of the RT-PCR assays used was 45.0. An in-house enterovirus real-time RT-PCR was used to test samples from patient 1. A commercial RT-PCR assay produced by Cepheid and commercialized by Orgentec (GP-EV-040, Orgentec, Trappes, France) was used to test samples from patients 2 and 3. Another commercial RT-PCR assay, Dia-ENT-050 (Diagenode, Seraing, Belgium) was used to test samples from patient 4.

§CSF sample was hemorrhagic (10,300 erythrocytes/mm²).
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References


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