CRIMSON PUBLISHERS
Wings to the Research

Developments in Clinical & Medical Pathology

Mini Review

ISSN: 2690-9731

Enterovirus 71 in Europe: A Briefing

Madeddu Silvia and Giuseppina Sanna*

Department of Biomedical Sciences, University of Cagliari, Italy

***Corresponding author:** Giuseppina Sanna, Department of Biomedical Sciences, University of Cagliari, Monserrato (CA), Italy

Submission: February 28, 2018; **Published:** March 22, 2018

Abstract

Enterovirus A71 (EV-A71) was first identified in California in 1969 and described in 1974 by Schmidt et al. Since then it has been implicated in more than 10 small and large outbreaks world-wide. Wide epidemic of hand, foot and mouth disease (HFMD), generally benign, occurred in Japan in 1973 and 1978. Important outbreaks with brain stem encephalitis and high mortality rates have been described in Europe in the 1970s (Bulgaria and Hungary in 1975 and 1978 respectively), in Malaysia in 1997 and Taiwan in 1998 and in Asia-Pacific region, including China and Korea. Recently, EV-A71 epidemics have been reported in European countries, such as the Netherlands, France, Spain. EV-A71 infection causes hand-foot-mouth disease, herpangina, fever and usually resolves spontaneously and do not need specific treatment, however, can sometimes induces a variety of neurological complications, including encephalitis, aseptic meningitis, pulmonary edema and acute flaccid paralysis that can be fatal. In this review we focus on enterovirus A71 infections, summarizing that one's occurred in Europe which have raised particular concern about the potential emergence of EV-A71 as a worldwide health threat.

Keywords: Enterovirus A71; Outbreaks; Clinical features; CNS involvement

Introduction

Enterovirus A71 (EV-A71) is a positive single-stranded RNA virus belonging to the Picornaviridae family, genus Enterovirus, species Enterovirus A (EV-A) that includes also Coxsackievirus A6 (CV-A6), coxsackievirus A16 (CV-A16), and 22 other serotypes [1]. EV-A71 and CV-A16 are the main causative pathogens of hand, foot and mouth disease (HFMD). HFMD is a highly contagious viral infection that usually affects infants and children younger than 5 years old and is characterized by fever, a maculopapular rash with blisters on hands, feet, ulcers inside or around the mouth. The incidence of HFMD caused by EV-A71 is less than that one caused by coxsackie virus A16, however, EV-A71 is a neurotropic virus, that occasionally involves the central nervous system (CNS), and induces different neurological complications that can even be fatal [2,3]. In recent years, there have been an increasing number of reports of HFMD outbreaks with fatal cases due to EV-A71 in various countries.

EV-A71 has been classified into 3 genogroups (A-C), 12 subgenogroups (A, B0-B5, C1-C5) [3] and 3 new genogroups (D-F), recently identified [4-6]. Only B and C genogroups are known to be associated with outbreaks. Subgenogroups B4, B5 and C4 are mainly restricted to Asian countries while C1 and C2 circulate in Europe [7-10] predominantly within the past 2 decades, and a recent introduction of C4 genotype has been reported [11]. Disease activity is generally seasonal, and infections occur in the summer and early fall in temperate areas of the world. EV-A71 cause a systemic infection after ingestion and replication in the gastrointestinal tract. The transmission route is predominantly via the faeco-oral route, but can also spread by hand contact with secretions and autoinoculation to the mouth, nose or eyes and in respiratory droplets. EV-A71 is easily transmitted in the developing countries because of crowded environments and poor sanitary conditions. In this review, we provide a short update about EV-A71 infections and earlier outbreaks in Europe.

Clinical Features, Laboratory Diagnosis and Treatment

EV-A71 clinical manifestations have included hand-foot-mouth disease, herpangina, fever and neurologic disease. HFMD mainly affects infants and children, high incidence and severity was shown in young debilitate children with weakened immune systems, rather than in adults [3,12]. The symptoms of HFMD in children are usually mild, comprising fever, loss of appetite, and a rash with blisters, which usually resolve spontaneously. However, EV-A71 can cause more severe neurological complications compared with other enterovirus serotypes, including brainstem encephalitis and acute flaccid paralysis [13-16]. Clinical reports highlight 4 phases in EV-A71: HFMD/herpangina, CNS involvement, cardiopulmonary failure (pulmonary edema and hemorrhage with left ventricular failure), and recovery (last phase). Mainly EV-A71 infections remain at phase 1, some progress to neurological complications, and a few advances to the most severe conditions, phase 3. Some survivors of third phase have long-term sequelae during convalescence (last

phase) [17]. Neurological symptoms or rash that usually affect patients under age 5, appear within 3 to 5 days after the onset of fever or skin lesions. However, patients show neurological manifestations without the skin or oral mucosal lesions typical of HFMD.

The diagnosis of EV based on real-time reverse-transcription PCR (RT-PCR) is a rapid sensitive and diagnostic approach which has become the standard method over virus isolation that is labour-intensive and time consuming. Specific RT-PCR assays have been developed for EV-A71 [18,19]. And directly performed from clinical specimens, on respiratory or rectal swabs, vesicle fluid, stool sample, and occasionally from skin-vesicle fluid, rather than cerebrospinal fluid (CSF), blood or urine. Despite the medical and socio economic impact of EV-A71 infections, antiviral therapy/treatment is currently ineffective. There is no enterovirus vaccine other than polio vaccine approved for human use in Europe. Vaccines against EV-A71 recently have been approved and are now available in China, it is an inactivated vaccine that is administered by injection.

Earlier Outbreaks in Europe

The number of EV-A71 -associated HFMD cases was relatively low in Europe compared to that one's in the Asia-Pacific region. After the Epidemic events occurred in Bulgaria and Hungary in 1975 and 1978, respectively, only sporadic with mild illnesses, mainly of FHMD has been associated to EV-A71 [8,20]. In a study from Norway [21], EV-A71 was detected in stool specimens from healthy children. Considering that HFMD is not under surveillance in Europe and healthy individuals are usually not the subjects under surveillance, the prevalence of EV-A71 may be underestimated [22,23]. In 2007, 58 cases of EV-A71 infection requiring hospitalization were reported in Netherlands after a period of low endemicity of 21 years. Strains of genogroup C1 and C2 were observed [22]. In Germany, from 2006 to 2015 an increased detection rates of EV-A71 was recorded and C2 was the predominant subgenogroup. Subgenogroups B5, C1, and C4 have also been identified, but less frequently. A fatal case of enterovirus A71 infection with pulmonary edema occurred in France in April 2007. The virus was identified as subgenogroup C2. In 2014, EV-A71 an outbreak of strain C2 was detected in a nursery school in Italy [24]. This identification has extended the information on the geographic diffusion and clinical relevance of EV-A71 in Europe. In Italy, there is no specific surveillance for EV infections, and the level of EV-A71 diffusion is not known as no information exists on the circulation of this virus. In Spain an outbreak of EV-A71 associated with neurological symptoms has been reported in 2016 and in Sweden, where surveillance was performed for all viral meningoencephalitis events, the EV-A71 displayed C1 genotype [20]. Increased numbers of EV-A71 detections reinforce the need for vigilance for enterovirus infections, especially cases that present with more severe clinical syndromes. Full molecular and biological characterization of the isolates from the current outbreaks will possibly enhance the understanding of the pattern of enterovirus A71 epidemiology in Europe.

Conclusion

EV-A71 was considered one of the top-five global infectious diseases to be kept under strict control, due to its propensity to cause large outbreaks and serious neurologic disease [25] for which there is currently no effective antiviral drug or vaccine. Before 2016, EV-A71 infections have only sporadically been associated with severe events in Europe. European countries should consider the importance of including EV infection in the differential diagnosis of neurological and serious respiratory diseases. Recently, in order to improve EV diagnostics, share data on severe EV infections and monitor the circulation of EV types, has been established European non-polio enterovirus network (ENPEN) [26]. Monitoring the circulation of EV-A71 will be useful to generate a database and integrate the data generated by European and extra-European laboratories. This network will possibly enhance the understanding of the pattern of enterovirus A71 epidemiology in Europe, ensure prompt and adequate diagnosis and initiate appropriate precautions, as well as to provide more accurate and complete epidemiological information.

References

1. Picornaviridae Study Group website. International Committee on Taxonomy of Viruses (ICTV).
2. He SJ, Han JF, Ding XX, Wang YD, Qin CF (2013) Characterization of enterovirus 71 and coxsackievirus A16 isolated in hand, foot, and mouth disease patients in Guangdong, 2010. Int J Infect Dis 17(11): 1025-1030.
3. Solomon T, Lewthwaite P, Perera D, Cardosa MJ, McMinn P, et al. (2010) Virology, epidemiology, pathogenesis, and control of enterovirus 71. Lancet Infect Dis 10: 778-790.
4. Deshpande JM, Nadkarni SS, Francis PP (2003) Enterovirus 71 isolated from a case of acute flaccid paralysis in India represents a new genotype. Curr Sci 84: 1350-1353.
5. Bessaud M, Razafindratsimandresy R, Nougairede A, Joffret ML, Deshpande JM, et al. (2014) Molecular comparison and evolutionary analyses of VP1 nucleotide sequences of new African human enterovirus 71 isolates reveal a wide genetic diversity. PLoS One 9(3): 90624.
6. Cardosa MJ, Perera D, Brown BA, Cheon D, Chan HM, et al. (2003) Molecular epidemiology of human enterovirus 71 strains and recent outbreaks in Asia Pacific region: comparative analysis of the VP1 and VP4 genes. Emerg Infect Dis 9(4): 461-468.
7. McMinn PC (2012) Recent advances in the molecular epidemiology and control of human enterovirus 71 infection. Curr Opin Virol 2(2): 199-205.
8. Bible JM, Iturriza-Gomara M, Megson B, Brown D, Pantelidis P, et al. (2008) Molecular epidemiology of human enterovirus 71 in the United Kingdom from 1998 to 2006. J Clin Microbiol 46: 3192-3200.
9. Mirand A, Schuffenecker I, Henquell C, Billaud G, Jugie G, et al. (2010) Phylogenetic evidence for a recent spread of two populations of human enterovirus 71 in European countries. J Gen Virol 91(9): 2263-2277.
10. Van der SS, van der AH, Lemey P, Uslu G, Koopmans M (2010) Evolutionary trajectory of the VP1 gene of human enterovirus 71 genogroup B and C viruses. J Gen Virol 91(8): 1949-1958.
11. Hassel C, Mirand A, Lukashev A, Terletskaia LE, Farkas A, et al. (2005) Transmission patterns of human enterovirus 71 to, from and among European countries, 2003 to 2013. Euro Surveill 20(34): 30005.
12. Kaminska K, Martinetti G, Lucchini R, Kaya G, Mainetti C (2013) Coxsackievirus A6 and hand, foot and mouth disease: three case reports of

How to cite this article: Madeddu S, Giuseppina S. Enterovirus 71 in Europe: A Briefing. Developments Clin Med Pathol. 1(1). DCMP.000503.2018.
DOI: 10.31031/DCMP.2018.01.000503

familial child-to-immunocompetent adult transmission and a literature review. Case Rep Dermatol 5(2): 203-209.

13. Hsing IH, Shih SR (2015) Neurotropic enterovirus infections in the central nervous system. Viruses 7(11): 6051-6066.

14. Melnick JL (1984) Enterovirus type 71 infections: a varied clinical pattern sometimes mimicking paralytic poliomyelitis. Rev Infect Dis 6(Suppl 2): 387-390.

15. Ryu WS, Kang B, Hong J, Hwang S, Kim J, et al. (2010) Clinical and etiological characteristics of enterovirus 71-related diseases during a recent 2-year period in Korea. J Clin Microbiol 48(7): 2490-2494.

16. Choi CS, Choi YJ, Choi UY, Han JW, Jeong DC, et al. (2011) Clinical manifestations of CNS infections caused by enterovirus type 71. Korean J Pediatr 54(1): 11-16.

17. Lee KY (2016) Enterovirus 71 infection and neurological complications. Korean J Pediatr 59(10): 395-401.

18. Ooi MH, Wong SC, Lewthwaite P, Cardosa MJ, Solomon T (2010) Clinical features, diagnosis, and management of enterovirus 71. Lancet Neurol 9(11): 1097-1205.

19. Perera D, Podin Y, Akin W, Tan CS, Cardosa MJ (2004) Incorrect identification of recent Asian strains of Coxsackievirus A16 as human enterovirus 71: improved primers for the specific detection of human enterovirus 71 by RT PCR. BMC Infect Dis 4(4): 11.

20. (2016) Rapid risk assessment-enterovirus detections associated with severe neurological symptoms in children and adults in European countries. European centre for disease prevention and control, Stockholm, Sweden.

21. Witsø E, Palacios G, Rønningen KS, Cinek O, Janowitz D, et al. (2007) Asymptomatic circulation of HEV71 in Norway. Virus Res 123(1): 1929.

22. Van der Sanden S, Koopmans M, Uslu G, Van der AH (2009) Dutch working group for clinical virology epidemiology of enterovirus 71 in the Netherlands, 1963 to 2008. J Clin Microbiol 47: 2826-2833.

23. Yip CC, Lau SKP, Woo PCY, Kwok YY (2013) Human enterovirus 71 epidemics: what's next? Emerging Health Threats Journal 6(1): 19780.

24. Medici MC, Tummolo F, Arcangeletti A, De Conto F, Chezzi C, et al. (2016) A cluster of Enterovirus 71 subgenogroup C2 in a nursery school, Italy, 2014. New Microbiol 39(4): 295-298.

25. Christian KA, Ijaz K, Dowell SF, Chow CC, Chitale RA, et al. (2013) What we are watching-five top global infectious disease threats, 2012: a perspective from CDC's global disease detection operations center. Emerg Health Threats J 6: 20632.

26. Heli H, Broberg E, Benschop K, Berginc N, Ladhani, et al. (2018) Recommendations for enterovirus diagnostics and characterisation within and beyond Europe. J Clin Virol 101: 11-17.