



SCIENTIFIC LETTERS

**Analysis of the clinical features of infections caused by enterovirus A71 (EV-A71) in Balearic Islands**<sup>☆</sup>



**Análisis de las características clínicas de las infecciones causadas por el enterovirus A71 (EV-A71) en las Islas Baleares**

Dear Editor:

Enteroviruses are a broad group of viruses with a wide geographical distribution. They predominantly affect children with respiratory, gastrointestinal, exanthematous, febrile and neurologic diseases. They are easily transmitted via person-to-person contact through faecal-oral route and have an incubation period of 1–3 days.<sup>1</sup>

Of the more than 100 known enteroviruses, enterovirus 71 (EV-A71) belongs to the *Enterovirus A* species, which comprehends more than 25 different serotypes, including coxsackievirus A16, which causes hand, foot and mouth disease (HFMD).<sup>1,2</sup>

Enterovirus 71 was first described in the context of outbreaks of infection with neurologic involvement between 1969 and 1972. Since then, it has been detected all over the world with a varying prevalence.<sup>1</sup> It is generally considered to cause mild or moderate respiratory disease, HFMD and neurologic illness of varying severity (meningitis, encephalitis or flaccid paralysis).<sup>1,2</sup> In some cases of HFMD, patients present with encephalitis at the level of the hindbrain, known as rhombencephalitis, that may cause severe neurologic sequelae.<sup>1,2</sup>

After the outbreak of neurologic illness caused by EV-A71 in Catalonia,<sup>3</sup> we thought it would be interesting to analyse the clinical characteristics of patients infected by this virus in the Balearic Islands.

We studied the presence of enteroviruses in respiratory samples (from pharyngeal swabs) of paediatric patients with clinical suspicion of acute respiratory tract infection (ARTI) between May 2015 and June 2016.

We performed viral detection by means of a gene amplification technique, a real-time RT-PCR assay capable of

detecting and differentiating 16 viruses in one step (Allplex<sup>®</sup> Respiratory Full Panel Assay, Seegene; South Korea). This assay can differentiate between enterovirus and rhinovirus, but cannot be used to serotype enteroviruses. Samples that tested positive for enterovirus were submitted to the Centro Nacional de Microbiología (National Centre of Microbiology, Madrid), where the final serotyping was performed.

A total of 5772 respiratory samples were analysed during the period under study, of which 2788 (48.3%) tested positive for a virus. Of the latter, 148 (5.3%) were positive for enterovirus, and 8 strains (5.4%) were serotyped as EV-A71 (amounting to 0.1% of all tested specimens and 0.2% of positive specimens). All cases were sporadic community-acquired infections that did not occur in the context of an outbreak.

Of the 8 patients, 4 (50%) were boys and 4 (50%) girls; their median age was 17 months (range, 5 months–3 years). The timeline of the cases was: 1 case (12.5%) in November 2015, and 1 (12.5%) in March, 2 (25%) in May and 4 (50%) in June 2016. Table 1 details the main diseases detected in these patients. Two patients (12.5%) had underlying diseases and 4 (50%) required hospital admission.

One patient presented with manifestations compatible with aseptic meningitis. The analysis of a cerebrospinal fluid specimen revealed a glucose concentration of 57 mg/dL, a protein concentration of 0.34 g/L, and counts of 5 red blood cells/ $\mu$ L and 40 white blood cells/ $\mu$ L (10% neutrophils and 90% lymphocytes). The results of PCR for the detection of neurotropic and respiratory viruses were negative.

Fifty percent of patients had viral co-infection, which involved enterovirus D68 in 3 (75%) and a bocavirus in 1; the percentage of co-infection was of 16.8% for the rest of the detected enteroviruses. All patients had favourable outcomes, and none died due to the viral infection or complications from it.

In our study, neurologic involvement was found in only 1 (12.5%) out of all patients with ARTI caused by EV-A71. This patient developed aseptic meningitis, which caused no further complications. The proportion of central nervous system infections in which this virus is involved ranges between 10% and 15%, and increases slightly during outbreaks.<sup>1,2,4</sup>

In recent years, several large-scale outbreaks of HFMD have been reported, especially in Asia, associated with central nervous system complications.<sup>1</sup> The virus has circulated less intensely in Europe, and in Spain there have been reports of outbreaks and sporadic cases of this disease.<sup>3–5</sup>

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**Table 1** Main characteristics of patients with infection by enterovirus A71.

Patient	Sex	Age	Symptoms	Underlying disease	Admission	Treatment
1	Female	1 year	Fever, cold symptoms	None	No	Paracetamol
2	Male	2 years	Fever, pharyngitis	None	No	Amoxicillin
3	Female	1 year	Fever, petechiae	None	Yes	Amoxicillin
4 <sup>a</sup>	Female	5 months	Fever, cold symptoms	None	No	Paracetamol
5 <sup>a</sup>	Male	1 year	Fever, cold symptoms	None	No	Paracetamol
6 <sup>a</sup>	Female	1 year	Fever, bronchitis	Asthma	Yes	Salbutamol, amoxicillin
7	Male	3 years	Fever, cold symptoms	Haemophagocytosis	Yes	Paracetamol, amoxicillin
8 <sup>b</sup>	Male	2 years	Fever, vomiting, ataxia Aseptic meningitis	None	Yes	Salbutamol, ceftriaxone

<sup>a</sup> Co-infection with EV-D68.

<sup>b</sup> Co-infection with bocavirus.

In the outbreak in Catalonia, there was a predominance of infections with neurologic involvement and in particular with rhomboencephalitis.<sup>3</sup> The sporadic cases detected in our study were associated with less severe disease, as most of them presented as acute respiratory tract infections (ARTIs), with no significant neurologic complications,<sup>6</sup> although the small number of cases did not allow reaching any firm conclusions. Some studies seem to suggest that there are different genetic lineages of EV-A71 that may determine its virulence.<sup>1,2,5</sup>

Given the sharp emergence of enteroviruses in respiratory and neurologic illnesses in the paediatric population in recent years, it is very important to carry out serotyping and follow-up studies of these infections.

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Jordi Reina<sup>a,\*</sup>, María Cabrerizo<sup>b</sup>, Francesc Ferrés<sup>c</sup>

<sup>a</sup> *Unidad de Virología, Servicio de Microbiología, Hospital Universitario Son Espases, Palma de Mallorca, Islas Baleares, Spain*

<sup>b</sup> *Unidad de Enterovirus, Centro Nacional de Microbiología, Madrid, Spain*

<sup>c</sup> *Sección de Urgencias, Servicio de Pediatría, Hospital Universitario Son Espases, Islas Baleares, Spain*

\* Corresponding author.

E-mail address: [jorge.reina@ssib.es](mailto:jorge.reina@ssib.es) (J. Reina).

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