

Acute neurological disease due to enterovirus: A review of clinical cases in a tertiary hospital in Andalusia after an outbreak in Catalonia[☆]



Patología neurológica aguda por enterovirus: revisión de casos clínicos en un hospital andaluz de tercer nivel tras brote epidémico de Cataluña

Dear Editor:

Enterovirus (EV) infections are common in childhood. They usually cause benign diseases such as herpangina or hand, foot and mouth disease, and are the most frequent cause of lymphocytic meningitis. Occasionally there is an outbreak that includes cases with neurologic involvement that manifests with acute flaccid paralysis and/or rhombencephalic involvement, as occurred in a 2016 outbreak in Catalonia.

Our aim was to describe the cases of the 4 patients admitted to our hospital with neurologic disease secondary to infection by EV between June and December 2016.

Table 1 shows the main characteristics of the patients. At admission, all of them presented with fever of several days' duration and a constellation of neurologic symptoms that ranged from depression and somnolence to instability, ataxia and involuntary tremors. All patients underwent a lumbar puncture, and microscopic examination of the specimens revealed lymphomononuclear pleocytosis in 3 cases (1, 2 and 3). Testing of cerebrospinal fluid (CSF), respiratory secretion and stool samples by polymerase chain reaction (PCR) detected EV in at least 1 of the samples in all 4 patients. The virus was detected in the CSF in only 1 case, and in the stool sample in all cases. In 3 of the 4 cases, cranial MRI revealed hyperintense lesions at the level of the rhombencephalon (Fig. 1). When it came to treatment, 2 patients received corticosteroids, 2 intravenous immunoglobulin therapy, and only 1 symptomatic treatment. All patients had favourable outcomes, as they were either asymptomatic or their symptoms had greatly improved compared to admission at the time of discharge.

In Europe, unlike China, infection by EV serotype 71 had been rare until recently and was associated with fever or hand, food and mouth disease. The virus is transmitted by the faecal-oral route or the oral-oral route. Certain EV serotypes, such as A71, are particularly neurotropic, and it has been hypothesised that neuroinvasion occurs through retrograde axonal transport.¹ Starting in March 2016, there were 100 cases in Catalonia that met the case definition criterion of "presentation with rhombencephalic involvement

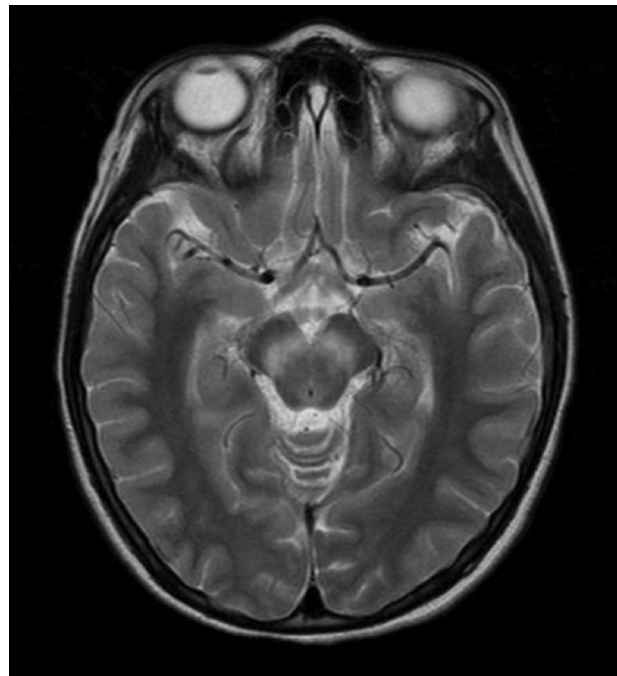


Figure 1 Case 2 patient: T2-weighted hyperintensity at mesencephalon.

or myelitis with detection of EV."² However, isolation of EV is not always associated with neurologic disease, and in fact, one study described that out of a total of 2788 respiratory samples from children with respiratory infections, 148 (5%) corresponded to EV infections, of which only 8 were by the EV-A71 serotype. Among these 8, there was only 1 case with neurologic involvement, which manifested as lymphocytic meningitis; this patient had a favourable outcome.³

In children, the presence of fever and neurologic involvement at the level of the rhombencephalon (myoclonic jerks, tremors and/or ataxia) and/or the medulla oblongata (cranial nerve involvement, abnormalities in swallowing or speech, apnoeic episodes and neurogenic pulmonary oedema)⁴ should be assessed by examination of the CSF, which usually reveals lymphocytic pleocytosis, and by performance of a MRI exam in the acute stage of disease, whose typical findings are the presence of hyperintense lesions on T2-weighted images, especially at the level of the pons, cervical spinal cord, mesencephalon, dentate nucleus and hypothalamus.⁵

The most sensitive and quick technique to establish the aetiological diagnosis, which is also currently the gold standard, is PCR. Despite the severity of the presentation, detection of EV in the CSF is rare. In fact, in our series only 1 of the 4 patients had a positive result, case 2, a female patient who had more severe neurologic manifestations. Therefore, suspicion of this disease should be approached by the collection of respiratory and stool samples, and detection of enterovirus alone does not suffice to rule out other diseases that may cause acute neurologic symptoms.

Unfortunately, we were unable to perform a serotype analysis of the enteroviruses found in our sample, and therefore, while the clinical and epidemiological data were mainly suggestive of EV-A71, we are unable to state that this was the involved type with certainty.

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Table 1 Main characteristics of cases of acute neurologic disease due to enterovirus.

| Case | Month | Age | Symptoms | Samples from which EV was isolated with PCR | Magnetic resonance imaging | Treatment | Outcome (1 month) |
|------|-----------|-----------|--|---|---|--|--|
| 1 | June | 10 months | 6-Day fever Somnolence Ataxia Tremors | Stools Respiratory | Normal | Symptomatic | Gradual improvement Full resolution of symptoms |
| 2 | June | 9 years | 4-Day fever Somnolence Ataxia Nystagmus Weakness Vomiting | Stool Respiratory CSF | T2-weighted hyperintensity in mesencephalon extending to the pons, with GM involvement | IVIg 1 g/kg/day, 2 days Methylprednisolone 30 mg/kg/day, 3 days | Improvement No resolution |
| 3 | September | 22 months | 2-Day fever Ataxia Vomiting Diarrhoea | Stool Respiratory | Altered T2-weighted signal with bilateral hyperintensity of GM in the mesencephalon | Methylprednisolone 2 mg/kg/day, 5 days | Gradual improvement Full resolution of symptoms |
| 4 | December | 21 months | 5-Day fever Somnolence Ataxia Conjunctivitis | Stool | T2-weighted hyperintensity at the medulla oblongata and junction of medulla and spinal cord | IVIg 1 g/kg/day, 2 days | Gradual improvement Full resolution of symptoms |

CSF, cerebrospinal fluid; EV, enterovirus; GM, grey matter; IVIg, nonspecific intravenous immunoglobulin therapy; PCR, polymerase chain reaction.

There is no specific treatment that is effective against infection by EV. Following the guidelines recommended by Spanish scientific societies, patients with severe symptoms received polyvalent immunoglobulins intravenously, as it has been proposed that they have an immunomodulator effect on the release of cytokines involved in the development of severe neurologic symptoms associated with infection by EV, although the evidence on the use of immunoglobulin is scarce and not from randomised controlled trials. Mega-dose corticosteroid therapy (30 mg/kg/day, 3–5 days) has been used in patients with severe neurologic involvement, although its use is not supported by evidence from randomised controlled trials⁶ and has been extrapolated from previous use in cases of acute myelitis.

Enterovirus A71 spread from the site of its earlier identification in Germany to France and Catalonia,² causing an outbreak that has not recurred in our province, which suggests that there are environmental and microbiological factors that play a role in the infection rate and virulence that have yet to be identified.

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Optimisation of measures to protect premature neonates of less than 35 weeks from the cold in the first hour of life^{☆,☆☆}



Optimización de medidas para evitar el enfriamiento en la primera hora de vida de los prematuros menores de 35 semanas de gestación

Dear Editor:

Postnatal stabilisation is a key aspect of the beginning of extrauterine life. The latest recommendations of the International Liaison Committee on Resuscitation (ILCOR, 2015)¹ and the Group on Neonatal Resuscitation of the Sociedad Española de Neonatología (Spanish Society of Neonatology, SENeo)² underscore the importance of maintaining a body temperature within the normal range (36.5–37.5 °C) in all newborns that are not experiencing asphyxia. Compared to adults, newborns need a higher temperature in the environment to maintain their body temperature, especially if they have been born preterm or in a compromised condition. Body temperature at admission in the neonatal unit is a predictor of morbidity and mortality and is especially relevant in extremely preterm newborns.³ Hypothermia causes hypoxia, metabolic acidosis, increased breathing difficulty and hypoglycaemia, and has been associated with an increased incidence of late-onset sepsis, retinopathy of prematurity, bronchopulmonary dysplasia, necrotising enterocolitis and intraventricular haemorrhage.^{1–5} It has been reported that in preterm newborns with birth weights less than 1500 g, for every degree Celsius that the admission temperature decreases below 36.5 °C, mortality increases by up to 28% and the risk of late-onset sepsis by up to 11%.³ Given the dire consequences of hypothermia, resuscitation

guidelines recommend early and effective interventions to prevent it in newborns.^{1,2,6} It is also important to avoid hyperthermia (a body temperature > 38 °C), as it has been associated with increased respiratory depression, neonatal seizures, early mortality and cerebral palsy.^{1,2}

The admission temperature of the patient must be recorded in the health record and is considered a health care quality indicator.

After reviewing the records of our hospital and finding that this recommendation was rarely met, in January 2016 measures were introduced to prevent decreases in body temperature in the delivery room and the first hour post birth, which are detailed in [Table 1](#). All the involved staff were informed of the proposed improvement measures (obstetricians, midwives, neonatologists, anaesthesiologists, nurses, health care technicians and maintenance staff). One year after introducing these measures, we conducted an observational study in which we reviewed the axillary temperatures recorded at admission in the health records of newborns delivered before 35 weeks' gestation. We excluded patients transferred from other hospitals. We defined normothermia as an axillary temperature of 36.5–37.5 °C.

In the previous 8 years (2008–2015), the mean axillary temperature at admission and the percentage of patients admitted with a normal temperature were similar, so we only show the results for 2015. [Table 2](#) compares a retrospective cohort of patients born at gestational ages of less than 35 weeks in 2015 with another prospective cohort of infants born in 2016, when the improvement measures aimed at maintaining normothermia in the first hour of life had already been introduced. We performed the statistical analysis with the SPSS[®] package version 20.0. We compared means using the Student *t* test for independent samples and percentages with the chi square test. We defined statistical significance as a *p*-value of 0.05 or less.

In years 2015 and 2016, 54.7% of admitted patients had been born before 35 weeks' gestation. In 2015, the mean axillary temperature at admission was 35.9 °C ± 0.7 °C, and only 20.9% of these patients had a normal body temperature at admission. However, in year 2016, after the introduction of the improvement measures, the percentage of patients admitted with a normal temperature rose to 58.1%, and the mean admission temperature to 36.8 °C, differences that were statistically significant. In the subset born before 32 weeks' gestation, a group in which neonatal resuscitation guidelines emphasise the importance of maintaining normothermia, the impact of the improvement measures was even greater, with the target temperature range achieved in

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