



# Enfermedades Infecciosas y Microbiología Clínica

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## Scientific letters

### Enteroviral meningitis in infants under 3 months<sup>☆</sup>



#### *Meningitis por enterovirus en niños menores de 3 meses*

In infants under 3 months of age, fever may be the main symptom or the only manifestation of a potentially serious disease, so differentiating between an invasive bacterial infection and other processes continues to be a diagnostic challenge. In recent years, polymerase chain reaction (PCR) molecular techniques have made it possible to carry out early and reliable aetiological diagnosis of some germs, especially viruses, modifying some aspects of hospital management.<sup>1</sup> Enteroviruses have become more important in recent years and during the epidemic period can account for up to 65% of paediatric hospitalisations with febrile syndrome.<sup>2</sup>

We present a prospective observational series of 39 infants under three months of age (16 neonates) with enterovirus meningoencephalitis diagnosed by cerebrospinal fluid (CSF) PCR admitted to a tertiary referral hospital over a period of four years (September 2012–September 2016). The specific real-time PCR technique was used (MutaREX<sup>®</sup> Enterovirus rt-PCR Kit, Immundiagnostik AG, Germany). Three patients with concomitant bacterial infection were excluded; all had *Escherichia coli* urinary tract infections.

The main clinical and analytical characteristics are shown in Table 1. The most common reason for consultation was isolated fever (89.7%), with 95% being generally well. In the CSF, the leucocyte count ranged from 2 to 1263 cells/ $\mu$ l (median 36 cells/ $\mu$ l), predominantly mononuclear cells. Pleocytosis was found in 64% of patients. The mean hospital stay was  $4.8 \pm 4$  days (median 4). Empirical antibiotic therapy was given to 79.5%, with mean treatment duration of  $4.2 \pm 5.7$  days (median 3), and this was discontinued in 50% of the patients the same day the PCR results were obtained. Clinical outcome was favourable in all cases, except for one patient who required intensive care for sepsis-like syndrome (hepatic failure, coagulopathy, thrombocytopenia) caused by Echovirus 11. Nasopharyngeal aspirates were requested in 26 patients for viral analysis, and enterovirus was isolated in 73% of the samples.

No statistically significant results were obtained when comparing neonatal patients (<28 days) with the rest of the sample, except for less development of exanthema in the neonates group (21.7% vs 0%,  $p = 0.046$ ).

The incorporation of molecular techniques into clinical practice has allowed many conditions previously classified as fever without a source or aseptic meningitis to be identified as enteroviral infections. It has previously been shown that CSF enterovirus PCR

**Table 1**

Clinical and analytical characteristics of infants aged <3 months with enteroviral meningoencephalitis.

<i>Gender, male</i>	22 (56.4%)
<i>Age, days</i>	40 $\pm$ 23
<i>Neonate</i>	16 (41%)
<i>Prematurity (&lt;37 wk)</i>	6 (15.4%)
<i>Good overall status</i>	37 (95%)
<i>Peak temperature at onset</i>	38.3 $\pm$ 0.36
<i>Reason for consultation, fever</i>	35 (89.7%)
<i>Family epidemic environment</i>	22 (56.4%)
<i>Respiratory symptoms</i>	8 (20.5%)
<i>Gastrointestinal symptoms</i>	3 (7.7%)
<i>Exanthema</i>	5 (12.6%)
<i>Plasma</i>	
Leukocytes (/ $\mu$ l)	9.232 $\pm$ 3.128
CRP (mg/dl)	0.89 $\pm$ 0.98
PCT (ng/ml), n = 13	0.27 $\pm$ 0.37
Platelets (/ $\mu$ l)	364,000 $\pm$ 124,000
<i>CSF</i>	
Leukocytes in CSF (/ $\mu$ l)	178 $\pm$ 291
% MNC	61.4 $\pm$ 27.9
Proteins in CSF (mg/dl)	70.1 $\pm$ 47.7
Glucose in CSF (mg/dl)	50 $\pm$ 10.4

CRP: C-reactive protein; CSF: cerebrospinal fluid; MNC: mononuclear cells; PCT: procalcitonin.

Quantitative variables expressed as the mean and standard deviation. Qualitative variables expressed as “n” and percentage of the total sample.

testing is associated with a reduction in number of days in hospital and the use of antibiotics.<sup>1</sup> In our series, empirical antibiotic therapy was discontinued the same day the PCR was obtained in 50% of the cases, clearly demonstrating the potential benefits in terms of healthcare and financial costs.

In our sample, the patients did not have significant analytical abnormalities in blood and we confirmed that CSF pleocytosis is not a reliable marker of enterovirus infection in young children; this could be related to a weaker inflammatory response in infants to enterovirus infection.<sup>3,4</sup>

The positive nasopharyngeal aspirate cultures (73% in our series), not being decisive in therapeutic management during admission, indicate that the study of enterovirus in other organic fluids could be useful in the diagnosis of children with aseptic meningitis. Foray et al. compared the combined use of pharyngeal aspirate and CSF to improve detection of enterovirus in children with aseptic meningitis, detecting enterovirus in 75% of cases compared to 32% when they only analysed the CSF.<sup>5</sup> Another study during an outbreak of enterovirus-71 encephalitis in children found that it is not always detected in CSF, requiring the study of enterovirus in nasopharyngeal aspirate and/or faeces. Among the possible explanations are the lower viral load in CSF or the transient nature of enterovirus in the CSF.<sup>6</sup>

In conclusion, enteroviral meningitis is usually benign, even in young infants. We believe that the determination of enterovirus in CSF is advisable in the study of all febrile infants aged less than 3

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months in whom lumbar puncture is performed, even if they do not have pleocytosis. The use of molecular techniques could potentially contribute to reducing the number of days of unnecessary antibiotic therapy.

### Conflicts of interest

The authors declare that they have no conflicts of interest.

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## Acute fulminant hepatitis B during hepatitis C virus therapy with direct-acting antivirals in a patient co-infected with HIV<sup>☆</sup>



### *Hepatitis aguda fulminante por virus B durante el tratamiento del virus de la hepatitis C con antivirales de acción directa en paciente infectado con VIH*

Co-infection with hepatitis C (HCV) and B (HBV) viruses is common in clinical practice. We report a case of fulminant hepatic failure as a consequence of reactivation of HBV in a patient with human immunodeficiency virus (HIV) after HCV treatment.

This was a 53-year-old man diagnosed in 1998 with HIV infection following detection of pulmonary tuberculosis, with a good current response to antiretroviral therapy. In addition, he had chronic HCV genotype 1a infection and a history of previous HBV infection with positive IgG (anti-HBc IgG) core antibody, negative surface antigen (HBsAg) and antibodies (anti-HBs) and undetectable levels of HBV DNA, prior to initiation of treatment with direct-acting antivirals (DAA).

For his HIV infection, the patient had previously followed several treatment regimens with multiple failures and development of resistance. In 2011, he was prescribed treatment with tenofovir (TDF), abacavir and ritonavir-boosted atazanavir. The TDF was subsequently withdrawn after a slight worsening of his renal function, and the treatment was simplified to darunavir/cobicistat monotherapy. Since then, his viral load has been undetectable and his CD4 T-cell lymphocytes 500–800/mm<sup>3</sup> (CD4 T lymphocytes 800/mm<sup>3</sup> at most recent testing, prior to starting HCV treatment).

In October 2013, the patient started treatment for HCV according to the regimen pegylated interferon alpha-2a 180 µg, one weekly injection, and ribavirin 1000 mg daily (3-0-2), resulting in a 3-log decrease in HCV viral load by week 4 of treatment. The idea of adding first-generation direct-acting antivirals (telaprevir) was

proposed, but the patient refused to continue treatment because of poor tolerance to interferon.

In December 2015, his HCV viral load was 2,181,330.11 IU/ml with a liver stiffness measurement of 12 kPa. Since we already had DAA, he was started on treatment with sofosbuvir and ledipasvir for 12 weeks.<sup>1</sup> In week 2, his viral load had dropped to 284.51 IU/ml, by week 4 it was down to 30.45 IU/ml and by week 8 it was less than 15 IU/ml, with a sustained viral response at week 4 post-treatment.

A month later, the patient consulted with abdominal pain, nausea and jaundice, with total bilirubin 10.98 mg/dl, direct bilirubin 8.75 mg/dl, GOT 1025.40 IU/l, GPT 642 IU/l and INR 1.30. An HBV viral load of 6,193,455.96 IU/ml was found, with positive HBsAg, anti-HBc IgM and HBeAg serology. His HCV viral load remained undetectable, and hepatitis D virus was negative. We were therefore dealing with acute hepatitis caused by HBV.

The patient was started on treatment with entecavir (TDF had already been discontinued due to impaired renal function); however, he made poor progress and was included in a pre-liver transplant study. Despite the treatment, the patient became worse and was transferred to the Intensive Care Unit, where he continued to deteriorate and died as a result of acute liver failure.

The patient's HBV viral load was requested from samples stored during the HCV treatment; it was undetectable at the start of treatment and at week 2, but progressively increased to 98.80 IU/ml after 8 weeks of treatment and then to 82,700 IU/ml at week 4 post-treatment (Fig. 1).

The risk of reactivation of HBV in the context of immunosuppressive therapy is well known.<sup>2</sup> However, several cases of HBV reactivation following DAA treatment in HCV-HBV co-infected patients have been reported, and although most have had no clinical repercussions and a good response to nucleotide/nucleoside analogue treatment,<sup>3,4</sup> there was one 59-year-old patient with genotype 1b who developed acute fulminant HBV hepatitis in week 11 of treatment and had to have a liver transplant.<sup>5</sup>

In HCV-HBV co-infected patients, HBV DNA is usually low or undetectable,<sup>6</sup> although it can fluctuate, with HCV being the main cause of chronic liver activity. Different theories have been put forward to explain the inhibition of HBV replication in co-infected patients.<sup>7</sup> The first is that there seems to be a direct interaction between the two viruses, with HCV inhibiting HBV replication, but

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