1130-0108/2017/109/5/344-349
Revista Española de Enfermedades Digestivas

Rev Esp Enferm Dig
2017, Vol. 109, N.º 5, pp. 344-349

**ORIGINAL PAPERS**

# Autochthonous acute hepatitis E: an increasingly frequent diagnosis. Clinical-epidemiological analysis of our experience

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## ABSTRACT

**Background:** In Europe, acute hepatitis caused by the hepatitis E virus (HEV) traditionally was an infection found in people who had travelled to endemic zones, mainly Asia and Africa. However, a growing number of sporadic autochthonous cases are now being diagnosed in the Western world.

**Objective:** To analyze the cases of acute HEV hepatitis diagnosed in our setting, with the identification of the clinical-epidemiological characteristics.

**Material and methods:** We included the cases of acute HEV hepatitis diagnosed (positive anti-HEV IgM and/or HEV RNA present in serum) between January 2008 and December 2014. Different clinical, epidemiological and evolutive parameters were analyzed.

**Results:** A total of 23 patients were identified, all originating from Spain. Fourteen cases (60.87%) presented jaundice and marked cytolysis at the time of diagnosis (aspartate aminotransferase [AST] 1,106.91 U/l and alanine aminotransferase [ALT] 1,407.04 U/l). Twenty-two cases were regarded as autochthonous, and one patient had travelled to China three months before. The mean time to resolution was 11.2 weeks. Some autoimmune markers were positive in 43.5% of the patients. Two subjects were diagnosed with previous chronic liver disease and were classified as "acute-on-chronic liver failure" (ACLF), one died and the other underwent liver transplantation.

**Conclusion:** Acute HEV hepatitis in our setting is an autochthonous condition that is probably underdiagnosed, manifesting with jaundice and cytolysis. Autoimmune marker positivity is an epiphenomenon, which in some cases complicates the diagnosis.

***Key words:*** Hepatitis E. Acute hepatitis. Drug-induced hepatitis.

## INTRODUCTION

Hepatitis E is a generally self-limiting viral infection, although it can also lead to fulminant liver failure or become a chronic condition. An estimated 20 million cases of hepatitis E infection occur worldwide each year, with over three million cases of acute hepatitis (1).

The hepatitis E virus (HEV) is a small RNA virus belonging to the *Hepeviridae* family (2). It consists of an icosahedral particle lacking an envelope and is not inactivated by the mild alkaline and acid conditions of the digestive tract, a fact that facilitates fecal-oral transmission of the disease (3).

Epidemiologically, two presentations have been defined: epidemic and sporadic. Epidemic outbreaks, predominantly seen in young adults, occur in developing countries as a result of the fecal contamination of water, and are associated with important morbimortality. In contrast, sporadic presentations are usually seen in industrialized countries, affecting middle aged individuals who have visited endemic regions, or immigrants from these regions. However, there is a growing number of so-called "autochthonous" cases, suggesting the possible existence of a zoonosis with the presence of animal reservoirs. In this regard, HEV has been detected in serum and fecal material from rodents, poultry, sheep, cows, dogs, and particularly in pigs (4). Although transmission most often occurs via the fecal-oral route, there have been isolated reports of person-to-person transmission (5), as well as infection via blood transfusion (6,7) and meat consumption (8,9).

In Spain the estimated prevalence varies from 0.6% to 7.3%, depending on the region (3). In this regard, the highest prevalence occurs in Catalonia (10), where the presence of anti-HEV IgG has been reported recently in 19.96% of all Catalan donors (11). The estimated prevalence is 18.6% among those exposed to porcine livestock (4) and 10.4% in HIV-infected individuals (12). In the United States the reported prevalence is 6% (13), while in England the prevalence is only 0.04% among donors (7). The true number of infections is difficult to establish, since subclinical infections are common and probably outnumber clinical infections.

The present study evaluates the cases of acute HEV hepatitis diagnosed in our healthcare setting (León, Spain) and

*Received:* 10-02-2016
*Accepted:* 08-01-2017

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*Monteserín-Ron L, Jiménez-Palacios M, Linares-Torres P, Miguel-Peña A, Álvarez-Cuenllas B, Valverde-Romero ED, Fernández-Natal I, Jorquera-Plaza F. Autochthonous acute hepatitis E: an increasingly frequent diagnosis. Clinical-epidemiological analysis of our experience. Rev Esp Enferm Dig 2017;109(5):344-349.*

DOI: 10.17235/reed.2017.4258/2016

analyzes the most relevant clinical-epidemiological characteristics of the disease.

## MATERIAL AND METHODS

A retrospective study was made of all the cases of acute HEV hepatitis diagnosed between January 2008 and December 2014 in the Complejo Asistencial Universitario de León (Spain), derived from the Department of Digestive Diseases and the Emergency Care Department. The cases were documented from the data corresponding to the samples processed by the Microbiology laboratory during that period.

The diagnosis of hepatitis E was established by the presence of specific anti-HEV IgM and/or IgG antibodies using ELISA (DiaPro, Diagnostic Bioprobes) and/or Immunoblot (HEV Mikrogen). Likewise, in some cases the viral RNA was detected by nested PCR of the ORF 1 and ORF 2 regions (14). The serological study of markers corresponding to hepatitis A (anti-HAV IgM), hepatitis B (HBsAg, anti-HBc and HBV DNA) and hepatitis C (anti-HCV and HCV RNA) was carried out in all patients using chemiluminescence (Architect, Abbott) and COBAS® AmpliPrep/COBAS® TaqMan® for the PCR detection of HBV and HCV.

The diagnosis of acute HEV hepatitis was considered in all those patients presenting positive IgM and/or PCR test results, accompanied by elevated transaminase and bilirubin values. Fulminant hepatitis was defined as severe and acute deterioration of liver function, associated with encephalopathy in the absence of previous liver disease. It was characterized as "acute-on-chronic liver failure" due to the existence of severe and acute deterioration of liver function in the presence of a previous liver cirrhosis. The resolution of acute hepatitis was considered as the normalization of transaminases, and chronification of the disease in turn was defined as the alteration of the transaminase levels and RNA positivity for at least six months. We also recorded other variables at the time of diagnosis, such as patient age, gender, residential setting, citizenship, profession, travel to endemic zones, alcohol consumption, weekly consumption of pork, previous liver disease, previous transfusions, laboratory test data (ALT, AST, alkaline phosphatase, gamma-glutamyl transpeptidase [GGT], serum bilirubin, serum albumin, international normalized ratio [INR], platelet count, prothrombin time and autoimmune markers), and evolutive parameters (duration, treatment and chronicity).

Quantitative variables are reported as means and range, while qualitative variables are presented as absolute values and/or percentages.

## RESULTS

A total of 23 patients (11 males and 12 females) with a mean age of 65.35 years (range: 41-86) were identified during the study period. All the patients were from Spain, and 14 (60.87%) lived in a rural setting. A total of four subjects (17.39%) consumed > 80 g of alcohol/day, and five (21.74%) had previous alcohol-induced or autoimmune chronic liver disease. Only one patient had visited an endemic region (China) three months before. Table I shows the epidemiological characteristics of the sample.

Seven cases were diagnosed in the first three years of the study period (2008-2011), while 16 were identified over the next four years. One patient was anti-HEV IgM negative, with positivity for both HEV IgG and HEV RNA. The remaining patients were all anti-HEV IgM positive (95.65% of the sample), as determined on five occasions by Immunoblot testing. Hepatitis E viremia was only tested in ten cases in the National Center of Microbiology (Majadahonda, Spain), and was positive in all of them (43.9%).

Two patients showed positive anti-HBc serological tests. The rest of the hepatotropic virus tests proved negative. Some autoimmune markers proved positive in ten patients (43.48%). Drug-induced hepatitis was initially suspected in 23% of the cases.

Regarding the clinical presentation, 14 patients (60.87%) had jaundice at the time of diagnosis, with important cytolysis. The serum bilirubin, ALT and AST concentrations are shown in table II with the evolutive data. Only the patient who died had hepatic encephalopathy. No other extrahepatic manifestations were associated with the infection.

Four liver biopsies were performed. In one case the histological findings were consistent with hepatitis in the resolution phase, which also showed histological characteristics compatible with autoimmune hepatitis. The rest of the biopsies showed acute hepatitis with ductular reaction, cholestasis and lobular damage. The histological findings could not rule out acute viral hepatitis, drug-induced hepatitis or bile duct obstruction.

In case 21, in view of the persistence of high levels of bilirubin and cytolysis, treatment with ribavirin was started for 12 weeks, with subsequent HEV-RNA loss in several determinations. However, normalization of transaminase levels was not achieved, which remained in the order of five to ten times the upper limit of normality. Finally, acute HEV hepatitis was regarded as the triggering factor of associated autoimmune hepatitis.

Two cases corresponded to patients with previous chronic liver disease: one of them suffered alcoholic liver disease, Child A5 stage and died as a result of liver failure, while the other presented hydropic decompensation of the primary biliary cholangitis and finally underwent liver transplantation as he presented a Child C11 stage (patients nº 11 and 1 respectively).

## DISCUSSION

Infection produced by HEV has a worldwide distribution, and has been detected in all countries in which the disease has been studied. The incidence of HEV infection has increased in Spain in recent years (3,10,15), although the prevalence has remained stable. This is probably due to increased awareness and knowledge of the disease, as well as a greater availability of the means for detecting

**Table I. Epidemiological characteristics of the sample**

| *Case* | *Gender* | *Age* | *Residential setting* | *Profession* | *Comorbidity* | *Suspicious medication* |
|---|---|---|---|---|---|---|
| 1 | F | 41 | Urban | - | PBC | No |
| 2 | F | 55 | Countryside | Rancher | - | No |
| 3 | M | 68 | Countryside | Plumber | - | Pioglitazone |
| 4 | F | 79 | Countryside | Rancher | - | No |
| 5 | M | 56 | Countryside | Farmer | - | No |
| 6 | M | 78 | Countryside | Rancher | - | No |
| 7 | M | 51 | Countryside | Rancher | Alcoholic liver disease | No |
| 8 | M | 69 | Countryside | Railway man | - | No |
| 9 | F | 85 | Urban | Nun | - | Amoxicillin- clavulanic |
| 10 | M | 86 | Countryside | Gas station employee | - | Paracetamol |
| 11 | M | 48 | Urban | Construction worker | Alcoholic liver disease | No |
| 12 | F | 49 | Urban | Administrative | - | No |
| 13 | M | 66 | Countryside | Seller | Kidney transplant | No |
| 14 | F | 54 | Urban | Teacher | - | No |
| 15 | M | 74 | Countryside | Rancher | Alcoholic liver disease | No |
| 16 | M | 69 | Countryside | Carrier | Alcoholic liver disease | Ibuprofen |
| 17 | F | 74 | Countryside | - | - | No |
| 18 | F | 55 | Urban | Administrative | - | No |
| 19 | F | 76 | Countryside | Housewife | - | No |
| 20 | F | 69 | Countryside | - | - | Herbal product |
| 21 | F | 63 | Urban | Housewife | - | No |
| 22 | F | 84 | Urban | Housewife | - | No |
| 23 | M | 54 | Countryside | Railway man | Lymphoma | No |

M: Male; F: Female; PBC: Primary biliary cholangitis.

anti-HEV antibodies. This would explain why most of our diagnoses were made in the second half of the study period.

All patients were anti-HEV IgM or HEV positive RNA for diagnosis. However, it has been seen on some occasions that the conversion of anti-HEV-positive IgG to undetectable levels during the acute phase is strongly associated with the detection of acute HEV infection, and may be the only marker detected (16).

The HEV genotype was not considered in our study, although the cases isolated to date in Spain were genotype 3 (3), which infects both humans and animals (4,8,9). Most of the patients were from a rural setting, with a high weekly consumption of pork and increased contact with animals, which constitutes the main risk factor. Only one case was not considered to be autochthonous, since it involved a patient who had visited China three months before, even though the incubation period of the disease is 2-10 weeks (3). In any case, the genotype was not determined.

Hepatitis E infection in patients with chronic liver disease can give rise to serious liver decompensation with encephalopathy and renal failure, associated with increased morbimortality (17). The two cases that resulted in death and transplantation corresponded to patients with alcoholic liver cirrhosis and primary biliary cholangitis, respectively. Both cases were considered to represent acute-on-chronic liver failure (18).

The important presence of autoimmune marker positivity can complicate the diagnosis, and may be regarded as an epiphenomenon secondary to the viral reaction. A high prevalence of anti-HEV antibodies has been reported in patients diagnosed with autoimmune hepatitis (AIH) (19). No significant differences in clinical manifestations or outcome have been demonstrated with respect to anti-HEV antibody negative patients with AIH. However, it is recommended to rule out the presence of HEV infection in those patients with a poor response to immunosuppressive treatment.

In our study, HEV infection in one patient with persistent transaminase elevation and normalization of the bilirubin levels after ribavirin treatment was considered to have triggered associated AIH. The simplified AIH criteria were applied with a final score of +5 points (ANA 1:80, IgG ele-

**Table II. Analytical variables at diagnosis and evolution**

| *Caso* | *Jaundice* | *Bil. (mg/dl)* | *AST (U/l)* | *ALT (U/l)* | *PT (%)* | *Autoimmune markers* | *Ig (mg/dl)* | *Hospitalization* | *Resolution time (weeks)* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Yes | 15.0 | 141 | 67 | 67 | ANA 1:160<br>AMA 1:640 | IgG 2,385<br>IgM 400 | Yes | Transplant |
| 2 | Yes | 32.8 | 2,165 | 2,514 | 100 | - | - | Yes | 12 |
| 3 | No | 2.0 | 2,327 | 2,434 | 89 | - | - | Yes | 4 |
| 4 | No | 1.6 | 309 | 166 | 92 | ANA 1:80<br>TPO 150 | IgG 3,612<br>IgM 160 | No | 24 |
| 5 | Yes | 5.3 | 1,655 | 2,578 | 98 | - | - | No | 4 |
| 6 | Yes | 12.9 | 418 | 792 | 100 | - | - | No | 13 |
| 7 | Yes | 19.9 | 895 | 871 | 60 | cANCA 1:320<br>ANA 1:40 | IgG 2067<br>IgM 606 | Yes | 13 |
| 8 | Yes | 10.8 | 1,445 | 2,677 | 86 | cANCA 1:320 | IgG 931<br>IgM 232 | Yes | 2 |
| 9 | Yes | 11.6 | 1,104 | 1,258 | 79 | - | - | Yes | 2 |
| 10 | Yes | 13.8 | 773 | 1,948 | 69 | - | - | Yes | 10 |
| 11 | Yes | 58.6 | 3,088 | 1,841 | 28 | AML 1:640 | - | Yes | Exitus |
| 12 | No | 2.4 | 481 | 1,525 | 82 | TPO 306 | IgG 1221<br>IgM 274 | No | 8 |
| 13 | No | 1.1 | 224 | 280 | 85 | - | - | No | 24 |
| 14 | No | 0.2 | 73 | 68 | 65 | - | - | No | 13 |
| 15 | Yes | 18.2 | 1,801 | 3,258 | 77 | - | - | No | 5 |
| 16 | No | 2.5 | 1,424 | 1,115 | 78 | - | - | No | 4 |
| 17 | No | 2.9 | 157 | 183 | 98 | - | - | No | - |
| 18 | Yes | 4.4 | 1,605 | 2,351 | 100 | TPO > 1,000 | IgG 1,069<br>IgM 178 | No | - |
| 19 | No | 2.0 | 1,570 | 2,044 | 100 | pANCA 1:160 | IgG 1,129<br>IgM 110 | No | - |
| 20 | Yes | 9.3 | 865 | 1,367 | 98 | ANA 1:80 | IgG 774<br>IgM 132 | No | 24 |
| 21 | Yes | 21.4 | 2,554 | 1,945 | 79 | ANA 1:80 | IgG 2,764<br>IgM 236 | No | 18 |
| 22 | Yes | 4.3 | 255 | 885 | 100 | - | - | No | 8 |
| 23 | No | 0.9 | 130 | 195 | 97 | - | - | No | 13 |

Bil: Bilirubin; PT: Prothrombin time. Normal values: IgG (650-1,300), IgM (70-280), TPO (0-35).

vation and histology compatible with chronic inflammatory infiltrate of lymphocyte predominance, plasma cell islands and necrosis of the limiting plaque). Given the high suspicion, despite not meeting criteria, treatment with steroids was started, observing an initial decrease in transaminases, which led to a reduction of the dosage of corticosteroids, and thus, azathioprine was added. The patient is currently on immunosuppressive therapy and has maintained normal transaminase levels for more than 12 months.

An association between the occurrence of viral infections and a consequent development of AIH has recently been described (19). Currently, the pathogenesis of this entity is understood as the presence of a genetically predisposed subject that is exposed to an environmental factor that triggers the autoimmune process. Although there is no clear evidence for all of them, it appears that infection by Epstein Barr virus, hepatitis A virus, hepatitis E virus or cytomegalovirus, among others, could be related.

The main condition to be considered in the differential diagnosis is drug-induced hepatitis. The presence of acute HEV infection has been reported in 10-22% of patients with initially suspected DILI (drug-induced liver injury) (20). The figure in our series was 22%. Similar findings apply to the cases of acute hepatitis of indeterminate origin (21).

To date, the histopathological data have revealed no specific feature capable of aiding the diagnosis. However, in those cases where the etiology is not clear, particularly in the associated presence of autoantibodies or other previous autoimmune disorders, such data may be useful. In our series, three patients were biopsied in light of the negativity of the studies obtained at the time and the absence of clinical-analytical improvement (while HEV serology was pending) and to rule out HAI in the last case. None of them provided the final diagnosis. We therefore consider it advisable to perform HEV serological tests in acute hepatitis situations before deciding upon a histological study.

The infection is generally self-limiting and tends to heal spontaneously, though antiviral therapy may prove necessary in some cases, particularly when possible chronification is suspected, or in particularly severe acute infections. Pegylated-interferon has been shown to be effective, but seems to be related to rejection in transplant recipients. Ribavirin therefore seems to be the treatment of choice. The drug is well tolerated, and the main side effect is anemia, which requires dose reduction in 28% of the cases (22,23).

The chronification of HEV infection has been documented in immune suppressed individuals such as a transplant host receptor, patients receiving chemotherapy, or HIV-infected subjects, among others (12,24). However, a case has recently been reported in Spain involving an immunocompetent patient who developed chronic HEV liver disease and grade III/IV fibrosis in the liver biopsy (25). In our study, patient number 13 was undergoing immunosuppressive treatment for a kidney transplant since 2000, and number 23 was being followed up by Hematology for diffuse B lymphoma at the time of diagnosis. In spite of this, the infection did not progress beyond a period of six months in any of our patients. It was not possible to establish the resolution time in three cases that did not go to review and/or a control analysis was not carried out. Also, due to the small number of the samples, we cannot assess if the icteric forms present better or worse evolution as no significant differences were found between the two groups.

The main limitation of our study lies in its retrospective nature; it is not possible to correctly evaluate the epidemiological factors, which together with the absence of the genotype makes it difficult to clarify the etiology of the infection. However, those patients in contact with the rural environment or with previous history of chronic liver disease could be established as a risk group, in which, in the absence of another suspicious factor, the detection of HEV autoantibodies could be requested as the first step with the rest of the common serology tests.

An increase in the number of cases of the disease can be expected in the coming years, due to the growing number of immigrants from countries where the infection is endemic, tourist visits to such countries, and, particularly, the presence of zoonosis as the origin of autochthonous cases. Increased clinical suspicion and improved facilities for diagnosing the disease will also contribute to the increase in the number of cases. Thus, in our opinion, serological testing for HEV should be included in the differential diagnostic process in all cases of acute hepatitis of uncertain cause or of possible drug origin before a histological study is performed. Furthermore, special attention is required in patients who are particularly vulnerable to severe infection, such as solid organ transplant recipients.

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