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Acute hepatitis E in French patients and neurological manifestations

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SUMMARY

Objectives: Hepatitis E virus (HEV) is a major cause of acute hepatitis worldwide. However, our understanding of the source of contamination is incomplete and the frequency of neurological manifestations in still unknown.

Methods: 200 eligible cases reported to the French National Reference Center from January 2015 to December 2015 were prospectively included in this case-control study (1 case: 1 control, matched for sex, age and area of living) to investigate the risk of infection. We documented the factors associated with their HEV infection and clinical manifestations.

Results: The 200 HEV-infected patients included 137 who were immunocompetent and 63 immunocompromised. The factors associated with an HEV infection were contact with farm animals, eating pork liver sausage and eating unpeeled fruit. The 33 patients (16.5%) who reported neurological symptoms included 14 with neuropathic pain suggesting small fiber neuropathy, 9 with painless sensory disorders, 6 with Parsonage–Turner syndrome, one Guillain–Barre syndrome, one meningitis, one encephalitis and one diplopia. Neurological manifestations were more frequent in immunocompetent patients (22.6% vs 3.2%, $p < 0.001$).

Conclusions: This study highlights the risk of HEV transmission by the environment in industrialized countries. The higher frequency of neurological disorders in immunocompetent patients suggests pathophysiological mechanisms involving the immune system.

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Introduction

While hepatitis E virus (HEV) has been a major cause of hepatitis outbreaks due to drinking contaminated water for decades in developing countries,[1] it is now recognized as a major etiologic agent of acute hepatitis in industrialized countries.[1,2] In these countries, the virus typically affects middle-aged or elderly men and can cause severe hepatitis, particularly in patients with an underlying liver disease.[1] The major transmission routes in European countries are zoonotic. Veterinarians and farmers working with pigs are more likely to have anti-HEV antibodies prevalence than do blood donors indicating direct exposure to infected animals.[3,4] Eating contaminated food like undercooked pork products or game meat is probably a major mode of HEV transmission.[5–7] Lastly, the HEV genome and infectious virus have been found in sewage water and rivers, indicating that exposure to a contaminated environment could be another transmission route.[8,9]

Most HEV infections are asymptomatic and even symptomatic hepatitis E is usually self-limiting and of varying severity. The incubation period of acute hepatitis E is 3–6 weeks, followed by a short prodromal phase, and a period of symptoms similar to

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those of other acute forms of viral hepatitis including jaundice lasting days to several weeks. Infections can become chronic in solid organ-transplant recipients, patients with hematological malignancies on chemotherapy or undergoing hematological stem cell transplantation and HIV-infected patients with low CD4 T-cell counts.[1] However, the clinical symptoms of an HEV infection are not completely understood. Hepatitis E patients exhibit a range of extra-hepatic manifestations including haematological, renal and neurological symptoms. Both acute and chronic hepatitis E may be associated with neurological injuries such as Guillain–Barré syndrome, neuralgic amyotrophy and encephalitis,[10] but neither their overall frequency nor the frequency of each neurological syndrome have been assessed.

This study examines the clinical and epidemiological features of autochthonous hepatitis E in France. We have identified the risk factors involved in HEV infection and determined the frequency and characteristics of neurological manifestations associated with such infections.

Patients and methods

Study design

Eligible cases reported to the national Reference Center between January 2015 and December 2015 were prospectively included. We carried out a case-control study (1 case: 1 control) to identify the factors associated with an HEV infection, assuming that the most realistic correlation between the two groups for exposure to risk factors was 0.2. We wanted to obtain a minimum odds ratio of 2 between the two groups with an alpha risk of 5% and a power of 80%. Dupont's method indicated that samples of 200 cases and 200 controls were needed to verify these postulated risk factors that can vary between 20% and 60%. We matched each of 200 cases having an autochthonous HEV infection with 200 controls who had no markers of HEV, for sex, age and department of residence. The study was performed in accordance with French guidelines and with ethics approval (Number 13.526); patients and controls gave their informed consent.

Laboratory methods

Cases of HEV infection were identified by detecting anti-HEV immunoglobulin M (IgM) by HEV IgM Rapid Test (Wantai Biological Pharmacy Enterprise Co, China), ELISA HEV IgM (Wantai Biological Pharmacy Enterprise Co, China) or the EIAgen HEV IgM kit (Adaltis, France) and/or HEV RNA using an accredited ISO 15189 RT-PCR method.[11] The HEV genotype was determined by sequencing a fragment of the ORF2 genome[12] and by phylogenetic analysis based on the reference sequences proposed by Smith et al.[13] Matched controls were anti-HEV IgG and IgM negative using Wantai HEV IgG EIA kit (Wantai Biologic Pharmacy Enterprise, Beijing, PRC).

HEV questionnaire on clinical and epidemiological features

Each HEV-infected patient and his/her matched control was telephoned and asked to complete a structured, specific questionnaire that documented their demographic data (age, sex) and putative factors associated with HEV infection (see supplemental data S1). These factors included the transfusion, the type of dwelling (apartment, house, farm, institution), its wastewater system (main sewer, septic tank), their local environment (rural, close to a farm, urban), professional and extraprofessional activities (gardening, vegetable growing, hunting, contact with river, lake, swamp or sewage water). We recorded the subjects' contacts with pets, farm or wild animals and their eating habits. We also recorded the transfusion received by the patients. The questions concerned the consumption of meat including several pork products (ham, several types of sausages, pate, meat, bacon, chorizo and offal), shellfish, and uncooked and/or unpeeled vegetables or fruit. We also recorded the things that were eaten uncooked. Last, we recorded the source of drinking water (bottled, tap, private well).

Each HEV-infected patient was asked about his/her underlying diseases and clinical symptoms. If they declared any neurological symptoms such as headaches, sensations of electric discharge or burning/tingling sensations and muscular weakness according to a standardized survey, two neurologists, one of which was a neuromuscular disease specialist, conducted further investigations. They collected data from hospital and/or consultation reports, biological parameters, and questioned physicians and the patients themselves about their neurological symptoms. Patients with neurological manifestations completed a DN4 questionnaire to detect neuropathic pain.[14] It is a clinician-administered questionnaire consisting of 10 items. The scale has been widely used since 2005 because of its simplicity. It evaluates neuropathic pain following central and peripheral neurological lesions. It is also used for diagnostic purposes, allowing the clinician to determine if the pain is of neuropathic origin. We examined all further explorations performed in the participating centers, particularly imaging and electrophysiological studies. Their recovery at three months was estimated using the modified Rankin score (mRS).[15] The mRS is a disability scale with 7 possible scores ranging from 0 to 6 (0: no symptoms; 1: no significant disability, able to carry out all usual activities, despite some symptoms; 2: slight disability, able to look after own affairs without assistance, but unable to carry out all previous activities; 3: moderate disability, requires some help, but able to walk unassisted; 4: moderately severe disability, unable to attend to own bodily needs without assistance, and unable to walk unassisted; 5: severe disability, requires constant nursing care and attention, bedridden, incontinent; 6: dead. Standardized interviews to obtain a mRS score are recommended at 3 months (90 days) following hospital discharge.

Statistical analyses

The anonymized data from the completed questionnaires were recorded in Excel files and analyzed using Stata version 14 (StataCorp LP, College Station, TX, USA). The characteristics of individuals were compared using the χ^2 test for categorical variables and the Mann–Whitney U test for continuous variables. A statistically significant difference was defined as a P value < 0.05. We used a log-binomial analysis to identify variables independently associated with HEV infections (with variables having a p value < 0.10 after bivariate analysis) to study demographic and life style factors associated with HEV infection. Analysis was simplified by grouping together items involving the same theoretical risk, such as contact with pets like cats, dogs and birds under a single heading: "contact with pets". The consumptions of all forms of game - wild boar, deer and other game animals - also formed a single group, as did eating all forms of shellfish - oysters, mussels, scallops and other shellfish. The resulting reasonable number of clinically relevant variables selected enabled us to produce a convergent log-binomial model. Statistical significance was set at $p < 0.05$. We tested the interactions between all the variables included in the final model.

Results

Clinical and biological characteristics of HEV infections

We interviewed 200 cases (126 men) with an HEV infection contracted in France and their 200 controls between January 2015

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