

A comparison of hepatitis E and A in a teaching hospital in Northwestern Romania

Acute hepatitis E – a mild disease?

Abstract

Background & Aims: The incidence of locally acquired hepatitis E increased in recent years across Europe. There are only a few data on hepatitis E in Romania. The purpose of our research was to describe and compare hepatitis E and hepatitis A in adult patients.

Methods: We included all consecutive adult patients with hepatitis E (48) and hepatitis A (152) admitted in the Teaching Hospital of Infectious Diseases, Cluj-Napoca, Romania between January 2017 and August 2019.

Results: Hepatitis E incidence increased in 2018-2019 compared to 2017. The average age in hepatitis E patients was 50.6 versus 39.1 years in hepatitis A and two thirds of the patients in both groups were men. Compared to hepatitis A, patients with hepatitis E presented a milder course of disease with significantly less modified AST and ALT, bilirubin, prothrombin index and INR levels. We found a higher prevalence of comorbidities in hepatitis E patients adjusted for age & gender. Severe forms were found in 5 (3.3%) hepatitis A patients compared to 12 (25%) of hepatitis E patients, of which 3 died. Acute-on-chronic hepatitis E and immunosuppression were found in 6 and 5 patients, respectively.

Conclusions: Our study shows that hepatitis E incidence is increasing, being usually self-limited and milder compared to hepatitis A. Ribavirin treatment seems to be beneficial in patients with preexisting conditions.

Keywords

hepatitis e, hepatitis a, ribavirin

Background & Aims

Hepatitis E is an anthroponosis with typically mild evolution caused by the Hepatitis E virus (HEV), the *Hepeviridae* family, whose members infect humans and other mammals [1, 2]. Genotypes 3 and 4 are the most common in Europe, where the reservoir of infection is represented by asymptomatic but highly infectious pigs and wild boars (with reproductive index up to 8.8) [3–6].

Recent Romanian research found IgG HEV seroprevalence between 9.6% and 50% in farm, backyard pigs and wild boars, mostly genotype 3.

Romanian data on IgG HEV seroprevalence in humans is scarce: general population (5.9% - 28%) students and medical staff (12.5-13.98%) and patients with hepatitis B or C (12%). [7]

In Europe, transmission occurs through consumption of contaminated and undercooked pork or other meat products [8, 9] but other transmission routes have also been demonstrated (blood transfusions [10, 11]). Vegetable products are rarely associated with HEV in Europe, probably due to tight regulation of pig manure use in farming [8, 12]. Genotypes 3 and 4 may lead to chronic disease in immunocompromised patients [5, 13] yet, the majority of individuals are asymptomatic [14].

Genotypes 1 and 2 of HEV are obligate human pathogens that only cause acute disease and are more common in developing countries: Asia (genotype 1), Africa (genotype 2) and Central America (both), being transmitted through fecal-oral route and contaminated water [5].

The number of laboratory-confirmed cases increased across Europe since 2006 to even more cases than hepatitis A in Germany, UK and France [3] with an estimated two million locally acquired cases each year in Europe [5].

HEV infects the liver but may be present in other organs (brain, kidney, placenta) [15, 16] and HEV RNA becomes detectable in blood and feces after 2-3 weeks post-exposure and lasting 3-6 weeks. After an incubation of 15-60 days, liver enzymes, anti-HEV IgM and then anti-HEV IgG levels increase marking the clinical onset. Anti-HEV IgM antibodies may persist up to 1 year, anti-HEV IgG are long-lasting and in immunosuppressed patients, HEV RNA may be detectable for more than 6 months being considered chronic infection [5].

Risk factors for clinical manifestations include: male gender, age over 50 and preexisting liver disease [8, 17]. Acute-on-chronic liver failure has considerable fatality but benefits from antiviral treatment (ribavirin, interferon) [18, 19]. Occasionally, neurologic lesions in acute hepatitis E patients were reported and include: neuralgic amyotrophy, Bell palsy, Guillain-Barré syndrome, encephalitis and myelitis [20, 21]. Chronic cases (HEV RNA clearance failure after 6 months) have been reported in solid organ transplant recipients presenting long-lasting fatigue, elevated AST, ALT and γ -GT and sometimes negative anti-HEV IgM and IgG [13, 22, 23]. EASL recommends HEV testing in patients with the aforementioned pathologies, regardless of liver enzyme levels [5].

According to Romanian regulations, all confirmed and suspected cases of acute viral hepatitis (A to E) should be admitted and treated in an appropriate hospital.

Our objective was to describe all cases of HEV infection admitted in our hospital during the study period in comparison to all hepatitis A adult patients. We focused on patient characteristics that were available from our hospital's electronic records.

Methods

We performed a retrospective case-control study including all consecutive adult (>18 years old) hepatitis E and A cases registered in our hospital's (The Teaching Hospital of Infectious Diseases of Cluj-Napoca, Romania) electronic database starting from 2017 January 1 until 2019 August 30. Our institution serves the Transylvania region, but most patients live in Cluj County. All clinical departments within our hospital were considered similar regarding diagnosis and management of patients.

Hepatitis A and E were diagnosed using qualitative anti-HAV and anti-HEV IgM respectively using *bioMérieux VIDAS® Hepatitis panel* electrochemiluminescence immunoassays from blood samples [24].

All patients received appropriate supportive treatment according to our hospital protocols and general recommendations. We defined a severe case of hepatitis E if INR >1.5, hepatic encephalopathy grades 2-4 and/or comorbidities (acute-on-chronic liver disease, confirmed immunosuppression) or neurological manifestations were found (according to EASL guideline 2018) [5]. The therapeutic approach for these patients was supportive treatment *plus* ribavirin (600-800 mg/day). We defined severe cases of hepatitis A if INR >1.5, hepatic encephalopathy grades 2-4 were present. The therapeutic approach for these patients was supportive treatment *plus* plasma products. Therefore, additional treatment was ribavirin in hepatitis E patients and plasma products in hepatitis A patients.

All patient data were collected from electronic records. These include laboratory parameters at admission, final diagnosis according to ICM10 codes and doctors' description of each patient's presentation and evolution. For subjective parameters, the judgment of all doctors assigned to each patient was considered equivalent.

All patients signed an informed consent form. This study was approved by the ethics committee of our hospital.

Data were centralized in a spreadsheet, checked for consistency, anonymized and imported into R 3.6.1¹ on Linux where all subsequent statistical analyses were performed. We used absolute and relative frequencies to describe categorical data and means with standard deviations or medians with IQR and ranges to describe numerical data. Comparisons between hepatitis A and hepatitis E groups were performed using both univariate methods (t-test for continuous variables with normal distribution according to the Shapiro-Wilk test, Mann-Whitney test for continuous variables with non-normal distribution, Fisher test for binary variables) as well as two multivariate logistic regression models adjusting for (model 1): age & gender and (model 2): all variables taken into account. Prior to logistic models, right-skewed data were transformed using the decimal logarithm. All statistical tests used a significance cut-off value at $p < .05$.

Results

A total of 48 hepatitis E adult patients and 152 hepatitis A adult patients were included. No pregnant women were found in either group. No hepatitis E cases were registered in pediatric patients. Hepatitis E cases represented 9.62% from all registered cases of acute viral hepatitis during the study period, including legal minors (Figure 1). All hepatitis E cases are believed to be autochthonous but precise food items could not be reliably assessed.

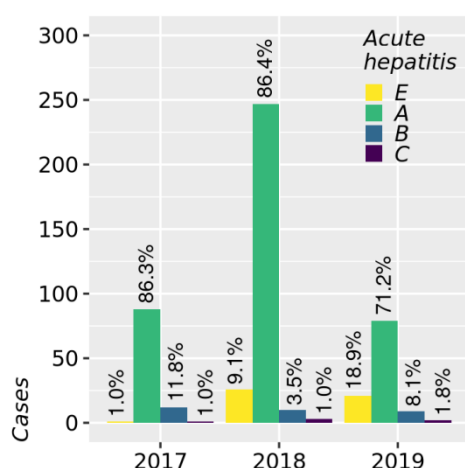


Figure 1. Distribution of acute viral hepatitis cases during the study period (2017 Jan 1 to 2019 Aug 30).

Most cases in both groups were male (M/F ratio: 1.47) and hepatitis E patients were significantly older than hepatitis A patients (Table 1).

Patients in both groups had similar median hospitalization length. The maximum duration was 43 days in a hepatitis E patient and 38 days in a hepatitis A patient (Table 1).

Hepatitis E patients had significantly milder abnormalities in laboratory values at presentation for direct & total bilirubin, AST, ALT, ALP, INR and prothrombin index and γ -GT (if adjusted for age & gender) (Table 1, Figure 2).

¹ R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>.

1 *Table 1. Hospitalization and laboratory parameters of the hepatitis E and A groups.*

Hepatitis (Group)		E n (%)	A n (%)	Univariate statistics	Adjusted OR ¹ p, [95% CI]
		48 (24.0)	152 (76.0)		
Gender	M	31 (64.6)	88 (57.9)	ns.	
	F	17 (35.4)	64 (42.1)		
Age at presentation (years)	μ ±DS	50.62 ±15.6	39.06 ±15.0	MW: p<.001	
	50+	28 (58.3)	31 (20.4)		
	[40,50)	7 (14.6)	28 (18.4)		
	[30,40)	7 (14.6)	52 (34.2)		
	[18,30)	6 (12.5)	41 (27.0)		
Hospital stay duration (days)	Med (IQR)	9 (7-14)	11 (8-14)	MW: ns.	ns.
Direct bilirubin (mg/dL)	Med (IQR)	1.24 (0.34-5.02)	4.9 (2.66-6.99)	MW: p<.001	0.194, p<.001, [0.09, 0.38] *
Total bilirubin (mg/dL)	Med (IQR)	1.73 (0.68-5.76)	5.87 (3.38-8.2)	MW: p<.001	0.182, p<.001, [0.08, 0.39] *
ALP (IU/L)	Med (IQR)	154.5 (119.25-192.75)	205 (159.25-260.5)	MW: p<.001	0.046, p=.003 [0.01, 0.34] *
γ-GT (IU/L)	Med (IQR)	229 (123.5-327)	246 (154.75-355.5)	MW: ns.	0.343, p<.048, [0.12, 0.99] *
AST (IU/L)	Med (IQR)	145.5 (69-676.75)	870 (304.5-1666.75)	MW: p<.001	0.112, p<.001, [0.05, 0.23] *
	> 350	17 (35.4)	99 (65.1)	OR=0.29, p<.001, [0.15, 0.58]	0.249, p<.001, [0.12, 0.51]
ALT (IU/L)	Med (IQR)	401 (122.75-886.25)	1817.5 (919.25-2801.75)	MW: p<0.001	0.045, p<.001, [0.02, 0.11] *
	> 350	26 (54.2)	132 (86.8)	OR=0.18, p<.001, [0.09, 0.37]	0.12, p<.001, [0.05, 0.27]
Prothrombin index (%)	Med (IQR)	88.25 (75.2-100.38)	72.7 (59.9-86.85)	T-test: p<0.001	1.039, p<.001, [1.02, 1.06]
	< 70	9 (18.8)	60 (42.0)	OR=0.32, p=.005, [0.14, 0.71]	0.268, p=.002, [0.11, 0.61]
INR	Med (IQR)	1.06 (0.99-1.13)	1.16 (1.07-1.31)	MW: p<.001	0.036, p=.002, [0.0, 0.26]
	> 1.5	4 (8.3)	16 (11.2)	ns.	ns.

¹: odds-ratio adjusted on age and gender; *: marked variables were transformed to base 10 logarithm prior to logistic regression due to skewness, therefore odds-ratios show tenfold increases/decreases in the respective laboratory parameters; μ ±SD: mean ±1 standard deviation; Med (IQR): median (inter-quartile range); MW: Mann-Whitney test; OR: odds-ratio with p-value and 95% confidence interval; ns.: not statistically significant at α=0.05; ALP: Alkaline Phosphatase; γ-GT: Gamma-glutamyl Transferase; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase.

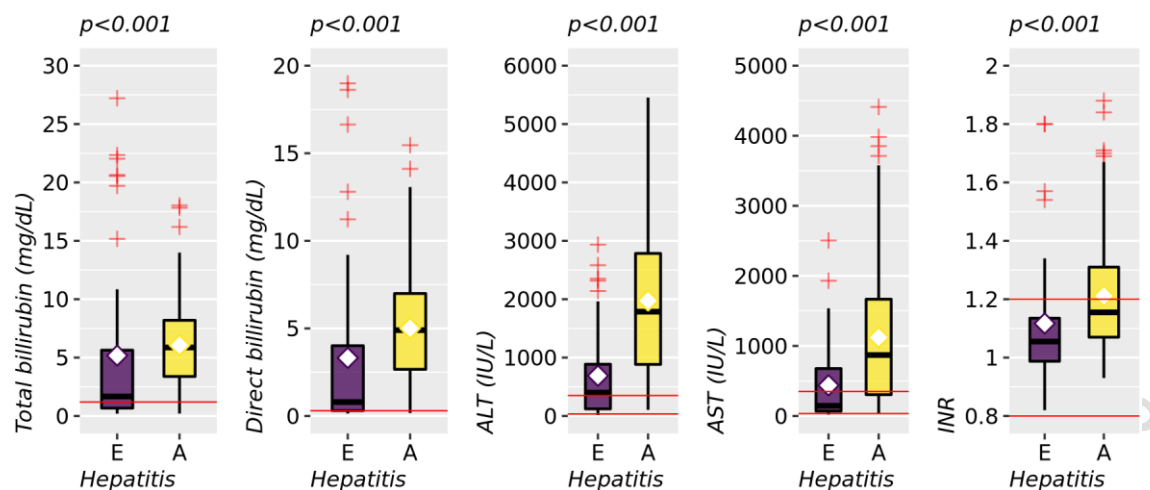


Figure 2. Several parameters differed significantly between hepatitis A and E groups. Laboratory reference ranges have been marked by horizontal red lines. Means are marked by diamonds. P-values from univariate Mann-Whitney tests

Table 2 summarizes chronic conditions associated with hepatitis E compared to hepatitis A: chronic liver disease, chronic kidney disease, neurologic disease, diabetes mellitus (univariate and adjusted for age & gender and other comorbidities).

Significantly more hepatitis E patients needed additional treatment (ribavirin) than hepatitis A patients (plasma w OR=6.8 (OR=4.9 adjusted for age & gender) (Table 2). All hepatitis E patients who received ribavirin had favorable evolution and were either discharged at home or to another department for specialized treatment of their comorbidities (Table 3).

The three deceased patients (6.25% of all hepatitis E patients and 23.1% of hepatitis E patients with preexisting liver disease) had hepatitis E infection superimposed on end-stage alcoholic liver disease and none of them received ribavirin. Two of them died because of bleeding from esophageal varices. The third patient, with chronic hepatitis B infection and *Streptococcus tholarensis* endocarditis died because of cerebral hemorrhage, septic cerebral embolism and multiple systemic organ failure (Table 4).

Table 2. Preexisting conditions and severity factors for hepatitis E and A patients.

Hepatitis (Group)	E n (%)	A n (%)	OR (univariate) p, [95% CI]	Adjusted OR (univariate) ¹ p, [95% CI]	OR (multivariate) ² p, [95% CI]
Chronic liver disease	13 (27.1)	6 (3.9)	9.04, p<.001 [3.21, 25.45]	7.19, p<.001 [2.53, 22.73]	6.21, p=.002 [2.0, 20.5]
Liver cirrhosis	6 (12.5)	1 (0.7)	21.57, p<.001 [2.53, 184.16]	12.5, p=.026 [1.86, 250]	
Hepatitis B coinfection	6 (12.5)	4 (2.6)	5.29, p=.014 [1.43, 19.60]	6.71, p=.007 [1.7, 29.41]	
Neurologic disease	6 (12.5)	2 (1.3)	10.71, p=.003 [2.09, 55.04]	9.52, p=.011 [1.89, 71.43]	4.76, p=.098 [0.8, 38.3]
Chronic kidney disease	5 (10.4)	2 (1.3)	8.72, p=.009 [1.63, 46.54]	5.18, p=.065 [0.99, 38.46]	6.175, p=.056 [0.99, 50.0]
Diabetes mellitus	10 (20.8)	9 (5.9)	4.18, p=.004 [1.59, 11.02]	2.04, p=.190 [0.69, 5.99]	3.39, p=.029 [1.1, 10.1]
Additional treatment*	9 (18.8)	5 (3.3)	6.78, p=.001 [2.15, 21.40]	4.93, p=.010 [1.49, 17.86]	4.47, p=.025 [1.2, 17.25]

¹: odds-ratio adjusted for age and gender; ²: odds-ratio in multiple logistic regression with all listed covariates (liver cirrhosis and hepatitis B coinfection included under chronic liver disease); * Additional treatment: hepatitis E – ribavirin, hepatitis A – plasma products.

Table 3. Hepatitis E patients who received ribavirin treatment. Summary of laboratory values (at admission / at discharge or transfer) and preexistent conditions

Age	Sex	Direct bilirubin (mg/dL)	AST (IU/L)	ALT (IU/L)	INR	Recommendation for ribavirin treatment according to EASL guidelines	Evolution	MELD score (3-months risk of death)
51	F	28.51 / 21.51	36 / 59	15 / 24	1.17 / 1.02	Breast cancer, liver, lung and bone metastases	Transfer to gastroenterology dept.	
21	M	0.25 / 0.19	19 / 20	75 / 35	0.92 / 0.99	Sagittal sinus thrombosis, bilateral facial palsy, one episode of seizures	Transfer to neurology dept.	
36	M	25.02 / 19.17	191 / 149	322 / 214	1.27 / 1.41	Chronic hepatitis B with advanced fibrosis	Transfer to gastroenterology dept.	23 (19.6%)
38	M	1.67 / 1.98	1010 / 147	1750 / 607	1.12 / 1.02	Hodgkin lymphoma with chemotherapy, bone marrow transplantation	Discharged at home.	
63	M	16.64 / 3.9	270 / 53	865 / 80	1.34 / 1.36	Coagulation deficiency factors VIII & IX, autoimmune hepatitis	Discharged at home	
64	M	0.27 / 0.32	321 / 74	1014 / 332	0.99 / 0.96	Retroperitoneal liposarcoma	Discharged at home	
69	M	1.31 / 0.81	570 / 85	436 / 141	1.12 / 1.01	Newly diagnosed colon cancer, diabetes mellitus	Discharged at home	
74	M	0.67 / 1.16	460 / 37	1013 / 219	1.06 / 0.96	Ethanol liver cirrhosis, Alzheimer and vascular and dementia, diabetes mellitus	Discharged at home	7 (1.9%)
75	M	24.1 / 7.11	645 / 44	374 / 23	1.57 / 1.38	Newly diagnosed ethanol liver cirrhosis and hepatocarcinoma	Transfer to gastroenterology dept.	24 (19.6%)

Table 4. Summary of laboratory values (at admission / last before death) and preexisting conditions in patients who died with acute hepatitis E.

Age	Sex	Direct bilirubin (mg/dL)	AST (IU/L)	ALT (IU/L)	INR	Preexisting conditions interpreted as causes of death	MELD score (3-months risk of death)
59	M	18.99 / 28.3	618 / 73	262 / 16.6	1.8 / 4.15	Hemorrhagic shock from esophageal varices, alcoholic liver cirrhosis (Child-Pugh C)	35 (52.6%)
61	M	12.8 / 23.71	1537 / 253	526 / 39.9	1.8 / 1.81	Hemorrhagic shock from esophageal varices, alcoholic liver cirrhosis (Child-Pugh C)	27 (19.6%)
65	M	4.92 / 14.51	157 / 23	50 / 56.4	1.54 / 1.37	Multiple system organ failure, alcoholic and hepatitis B viral cirrhosis (Child-Pugh B), endocarditis, cerebral embolism	31 (52.6%)

Elevated MELD scores were found in severe cases of HE with acute-on-chronic liver failure, including the three deceased patients (Tables 3-4).

Discussion

Our study showed not only an increased incidence of hepatitis E in recent years but also an unexpectedly high number of severe and/or lethal cases as an emerging source of morbidity and health care costs. This increase cannot be explained by better detection as the same protocol was used since 2016. Indeed, other European countries have experienced a similar trend with no definitive explanation. In several countries, hepatitis E turned into the most frequent cause of acute viral hepatitis [3, 25] though, in our hospital, a great number of hepatitis A cases were admitted in 2018, mainly in children and young adults.

The diagnosis and follow-up of hepatitis E include serological and PCR-based genotyping assays [5, 26]. In our patients, diagnosis was based on clinical criteria (suspicion of acute viral hepatitis or elevated liver enzymes) and serological testing, ready within 1-2 days. All new acute cases were tested for viral hepatitis A-E on the same laboratory request according to the hospital protocol.

Regarding HEV seroprevalence studies in Europe, no gender difference was found, but acute infection has a higher incidence in men, similar to our study [8, 27]. No definitive explanation has been provided but behavioral factors, food preference and comorbidities (such as alcoholism and chronic liver disease, more prevalent in men [28, 29]) may have contributed to it.

In our sample, hepatitis E affected only adults, with a median age of 52, similar to acute hepatitis B and C [28, 30, 31], while hepatitis A is found mainly in children and young adults [28, 30]. This imbalance may be attributed to both preexisting liver conditions as well as alimentary habits.

Since low infecting doses tend to cause asymptomatic infection [5, 32], clinical manifestations may be associated with either larger meals or highly contaminated food items.

Preexisting conditions are associated with clinical manifestations of hepatitis E. Acute hepatitis E may develop as acute-on-chronic liver disease with high fatality rates [5, 14]. Diabetes mellitus may slow-down liver regeneration and may cause immunosuppression [33]. We found more chronic conditions in hepatitis E patients compared to hepatitis A which may explain the

higher prevalence of severe clinical course and a higher fatality of hepatitis E irrespective of age and gender.

Generally, hepatitis E is a mild disease needing only supportive treatment. Severe, immunocompromised patients and patients with acute-on-chronic liver disease are candidates for etiologic treatment with ribavirin and PEGylated interferon-alpha, with expected favorable results [5, 34].

Among the 9 patients who received ribavirin, significant improvement was found in all cases; patients were either discharged at home or transferred to other departments for further care of their comorbidities. Acute-on-chronic liver failure was demonstrated in 3 of the treated cases, 5 other cases had immunologic deficiencies and another one presented with neurologic manifestations that triggered the search for hepatitis E infection.

The three deceased patients with acute-on-chronic end-stage liver disease with fulminant evolution and/or severe comorbidities did not receive etiologic treatment because of severe thrombocytopenia.

Only 5 hepatitis A cases (3.3%) developed severe disease with coagulation abnormalities and received plasma products, all with favorable outcome. Overall, more hepatitis E cases required additional treatment compared to hepatitis A despite apparent milder disease.

Our study had several limitations. Genotyping was not possible, we presumed that genotypes 3 and 4 are involved, as showed the studies performed in Romania and elsewhere in Europe [5, 7]. No reliable data on our patient's alimentary habits was available but the assumption is that pork products are responsible for most cases in a similar manner to other European countries [8]. Follow-up was not insured in all cases, which may have been valuable in measuring the rate of chronic HEV infection.

Conclusions

An increased number of hepatitis E cases were admitted to our hospital in the last two years. Hepatitis E was generally milder than hepatitis A, more frequently found in older patients with preexisting conditions. Ribavirin treatment seems to be beneficial in patients with acute-on-chronic liver disease and immunosuppression.

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