# Epidemiological characteristics and clinical manifestations of hepatitis E virus infection in Bulgaria: A report on 20 patients

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**SUMMARY**

**Introduction** Hepatitis E is one of the leading clinical manifestations of acute viral hepatitis in developing countries. In industrialized countries, during the past several years, sporadic "autochthonous" cases of HEV infection have been increased.

**Objective** The aim of this study was to analyze the epidemiological, clinical and laboratory features of HEV infection among patients hospitalized at the Department of Infectious Diseases in Military Medical Academy, Sofia, Bulgaria.

**Methods** A retrospective study of 806 cases of acute viral hepatitis was performed at the Department of Infectious Diseases in Military Medical Academy, Sofia, Bulgaria, between December 2004 and September 2012. The etiological diagnosis was established by ELISA. The statistical analysis was performed using Excel 2007 (Microsoft, Redmond, Washington, USA) and SPSS Statistics 19.0 (IBM Corp., Armonk, New York, USA).

**Results** Specific reaction to anti-HEV-IgM and anti-HEV-IgG antibodies were detected in 20 (2.48%) of 806 patients. The most observed clinical presentations were jaundice (85%), fatigue (85%), anorexia (65%), abdominal discomfort (55%) and fever (40%). The mean values of aspartate transaminase and alanine transaminase were 521 IU/l and 881 IU/l, respectively. The cholestasis was slight, marked with mean values of gamma-glutamyl transferase and alkaline phosphatase, respectively 418 IU/l and 486 IU/l.

**Conclusion** We report twenty autochthonous sporadic cases of acute infection with HEV. The zoonotic etiology of the virus as well as the foodborne transmission of the infection is discussed. We found that aging and pre-existing underlying diseases are risk factors for a severe course of the HEV infection.

**Keywords:** autochthonous HEV infection; clinical course; biochemical parameters

## INTRODUCTION

In India, in late 1970, there was evidence of waterborne epidemics of enterically transmitted viral hepatitis distinct from hepatitis A [1]. The new form of non-A, non-B hepatitis came to be known as epidemic non-A, non-B hepatitis or enterically transmitted non-A, non-B hepatitis [2]. Subsequently, the name was changed to Hepatitis E (HEV) [3]. It is a non-enveloped RNA virus with icosahedral particles of around 32 nm diameter [3, 4]. HEV is classified in the genus *Hepevirus*, family *Hepeviridae* [5, 6]. The virus has four genotypes, but only one serotype [7]. Genotype 1 and 2 infect humans, whereas 3 and 4 infect humans, pigs and other mammalian species [7]. HEV genotype 1 is responsible for most endemic and epidemic cases of the infection in Asia [8]. Genotype 2 is prevalent in Central America and Africa, whereas genotype 3 is mostly detected in Europe and North America [8, 9]. Genotype 4 is most common in Eastern Asia [10]. Probably HEV infection is the most common cause of acute hepatitis and jaundice in the world [8, 11]. It is endemic for several Asian and African countries [9]. In the developing countries HEV is a result of a waterborne infection and spread zoonotically in industrialized countries or associated with travel to endemic areas [8]. In the developed countries, during recent times, the number of HEV infection is witnessing an increase. It is associated with sporadic cases, occasional small foodborne infection related to autochthonous hepatitis E, assumed to be caused by zoonotic spread of the infection from wild or domestic animals [12].

## OBJECTIVE

The aim of this study was to analyze the epidemiological, clinical and laboratory features of HEV infection among patients hospitalized at the Department of Infectious Diseases in the Military Medical Academy, Sofia, Bulgaria.

## METHODS

Using records of the clinical histories, an epidemiological questionnaire, medical history, risk factors, comprehensive physical examinations and clinical monitoring during the hospital

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stay were obtained. Various laboratory tests including blood count, erythrocyte sedimentation rate (ESR), urine analyze, biochemical indicators as bilirubin (total and direct fraction), serum transaminases (aspartate transaminase [AST] and alanine transaminase [ALT]), cholestatic enzymes (gamma-glutamyl transferase [GGT] and alkaline phosphatase [AP]), glucose level, creatine, urea, total protein and albumin were performed. Hemostatic functions like fibrinogen levels and international normalized ratio (INR) were monitored. In some cases, serum cholinesterase and ammonia levels were measured to exclude hepatic encephalopathy and possible impending hepatic coma. Computer tomography (CT) was performed in cases with difficulties and underlying diseases, while abdominal ultrasound was done in all cases. The etiological agent of the infection was established by serological tests enzyme-linked immunosorbent assay (ELISA). Using ELISA, all serum samples were screened for hepatitis A virus (HAV), hepatitis B virus (HBV) and hepatitis C virus (HCV) as the first line. All those who tested negative for HAV, HBV, and HCV were then examined for Epstein–Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV) and Q-fever when clinical, epidemiological and laboratory features were suspicious.

The last step of diagnostic protocol was to test for HEV. The presence of specific IgM and IgG against HEV in case of clinical and laboratory data for acute hepatitis, confirmed the diagnosis of acute infection with HEV. We conducted the following serological tests: MP Diagnostics HEV IgM ELISA 3.0 (MP Biomedicals Asia Pacific Pte. Ltd., Singapore) and MP Diagnostics HEV ELISA (MP Biomedicals Asia Pacific Pte. Ltd., Singapore).

The first test: MP Diagnostics HEV IgM ELISA 3.0 is an enzyme-linked immunosorbent assay intended for the detection of IgM antibodies to HEV in human serum or plasma. This assay utilizes a highly conserved conformational epitope derived from open reading frame 2 (ORF 2) of the virus. The test has a positive predictive value of 94.9% and a negative predictive value of 98.7%, with sensitivity of 98.0% and specificity of 96.7%. Limitation of the test is that a negative result does not exclude the possibility of exposure to or infection with HEV.

The second test: MP Diagnostics HEV ELISA is an enzyme-linked immunosorbent assay intended for the detection of IgG antibodies to HEV in human serum or plasma. The assay utilizes the detection of presence of HEV antibodies. The presence of specific antibodies is indicated by the presence of blue color after substrate addition. The intensity of the color is measured spectrophotometrically at 450 nm and is proportional to the amount of antibodies present in the specimen. The presence or absence of IgG antibodies specific for HEV is determined by relating the absorbance of the specimens to the cut-off value of the plate. It is calculated as 0.500 + the mean absorbance of the non-reactive control.

For the classification of the clinical forms (mild, moderate and severe) we used a combination of clinical manifestation and laboratory abnormality. Mild form: previously healthy person, discreet clinical symptoms, anicteric clinical forms or slight elevation of bilirubin up to 75 μmol/l, mild cytolytic syndrome with transaminases up to 1,000 IU/l, cholestatic enzymes are normal or slightly elevated, normal hemostasis and quick recovery. Moderate form: marked clinical presentation with prolonged anorexia, fatigue, and jaundice on the background of underlying diseases. The value of bilirubin is between 75 μmol/l and 250 μmol/l, marked cytolysis with transaminases up to 2,000 IU/l, elevated cholestatic enzymes. The recovery is more prolonged. Severe clinical form: elderly person with previous liver illness and/or underlying diseases, co-infection with other hepatotropic virus. Clinical manifestation is characterized by fever, anorexia, vomiting, fatigue, weakness, drowsiness, severe jaundice, lethargy and/or other signs of encephalopathy. The value of bilirubin is high and amounts to more than 250 μmol/l, extreme level of transaminases above 2,000 IU/l, elevated cholestatic parameters, hemostasis disorder with prolonged prothrombin time and elevated INR, and/or other signs of liver failure. Increased probability for poor outcome or other complications is present.

Statistical analysis was performed by Excel 2007 (Microsoft, Redmond, Washington, USA) and SPSS Statistics 19.0 (IBM Corp., Armonk, New York, USA). Friedman test and Wilcoxon signed-rank test were done to estimate the p-values. When $p<0.05$, the result is statistically significant. The biochemical parameters between men and women were compared using Mann–Whitney test. The correlation between age and biochemical indicators was analyzed by Spearman's correlation coefficient.

## RESULTS

During the period of eight years, 6,774 patients were admitted to the Department of Infectious Diseases. Of these, 806 (11.9%) had clinical and laboratory data for acute hepatitis. The distribution of the various acute hepatitis etiological agents among these 806 cases was as follows: 16.13% HAV, 12.03% HBV, 2.23% HCV, 5.33% EBV, and 1.74% CMV. The undiagnosed hepatitis was 484 cases or 60.05% of all hepatitis. HEV was found in 20 patients with acute hepatitis. This is 2.48% of cases with acute hepatitis and 0.29% of all hospitalized patients within this period. Of these 20 patients, 14 (70%) were males. The mean age was 51 years (range 28–84 years). All patients were Caucasian. Sixteen (80%) of them lived in an urban area. None of them had contact with pigs, pig-breeding farms or slaughterhouses. However, all of them reported eating pork products as preferable meat.

The yearly incidence of HEV infection within this eight-year period is as follows: one case in each of 2004, 2005, 2006, and 2008; none in 2007; two cases in each of 2009 and 2012; six cases in each of 2010 and 2011.

The main symptoms and syndromes were dark urine, fatigue and hepatomegaly. The established clinical and physical data are presented in Table 1. The abdominal ultrasonography confirmed the enlargement of the liver in all cases.

Among laboratory parameters, special attention was directed toward bilirubin, serum transaminases and cho-

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lestatic enzymes. The values of these liver enzymes and bilirubin were measured at the time of admission, on the seventh day of hospitalization and on the day of discharge. The trend of cholestatic enzymes was done twice at the first and the last day of hospitalization. The mean values and the dynamics throughout hospital stay are presented in Table 2. A sex-dependent variation of the laboratory results was also assessed.

**Table 1.** Clinical characteristics and physical findings in 20 patients with acute hepatitis E virus (HEV) infection

| Variables | | Number of patients | % |
|---|---|---|---|
| Sex | Male | 14 | 70 |
| | Female | 6 | 30 |
| Age (years) | | 53±16* | - |
| Patients with previous non-liver diseases | | 8 | 40 |
| Patients with previous/present liver illness | | 12 | 60 |
| Clinical manifestations | Abdominal pain | 11 | 55 |
| | Anorexia | 13 | 65 |
| | Dark urine | 16 | 80 |
| | Fever | 8 | 40 |
| | Decolorized stool | 6 | 30 |
| | Muscle pain | 6 | 30 |
| | Nausea | 8 | 40 |
| | Scleral icterus | 10 | 50 |
| | Vomiting | 5 | 25 |
| | Fatigue | 17 | 85 |
| | Headache | 1 | 5 |
| | Pruritus | 2 | 10 |
| | Diarrhoea | 1 | 5 |
| Physical examination | Jaundice | 17 | 85 |
| | Hepatomegaly | 17 | 85 |
| | Splenomegaly | 9 | 45 |

* mean value ± standard deviation

According to Table 2, a significant elevation of serum transaminases was present (AST – 13-fold that of upper limit of normality [ULN] and ALT – 22-fold of ULN). The ratio AST/ALT was less than 1, typical for viral hepatitis. There was a mild increase of cholestasis enzymes (GGT – 8.4-fold of ULN, and AP – 1.62-fold of ULN). The laboratory results showed evidence of hyperbilirubinemia corresponding to the clinical manifestation of jaundice.

Serological investigations showed the following results: in all patients, data indicated HEV infection (anti-HEV IgM and anti-HEV IgG positive results); anti-HAV total was established in 25%; anti-HBs in 5%; anti-HBs and anti-HBc total occurred in 20%; acute HBV infection in early reconvalescent phase (HBsAg, anti-HBc IgM, and anti-HBe) in 5%; and anti-HCV in 5%.

The clinical course of HEV infection was mild in 13 patients, moderate in four, and severe in three patients (Table 3). A connection between pre-existing diseases, co-infections, and previous liver diseases with the severity of the HEV infection was established. Ten patients had underlying diseases (cardiovascular, hepatic and endocrinology disorder) and 12 had clinical histories of serious hepatic diseases in the past and/or in the present (previous HAV infection, preceding HBV infection, malaria, hepatic resection with cholecystectomy and toxic hepatitis). The severe cases are presented below.

The first case was a co-infection of HEV and HBV in a 30-year-old woman, with symptoms of fever, anorexia, nausea, vomiting, and jaundice. Transitory macula rash appeared on the feet, hands and knees in the beginning of the

**Table 2.** Comparison of weekly measurements of liver function tests in patients with HEV infection

| Variables | Normal range | Sex | Weekly measurements (mean ± SD) | | | p-value |
|---|---|---|---|---|---|---|
| | | | Admission | 7th day | Discharge | |
| AST (IU/l) | 5–40 | M | 1,324.9±1151.4 | 453.1±218.6 | 138.3±187.1 | <0.01 |
| | | F | 531.0±315.1 | 265.0±171.8 | 57.0±27.7 | <0.01 |
| ALT (IU/l) | 5–40 | M | 1,851.8±1290.5 | 949.2±625.1 | 190.5±103.7 | <0.01 |
| | | F | 838.3±1034.6 | 431.5±349.0 | 113.3±53.0 | 0.03 |
| GGT (IU/l) | 10–50 | M | 692.9±969.7 | ND | 277.6±238.5 | <0.01 |
| | | F | 135.0±110.3 | ND | 129.7±95.9 | 0.35 |
| AP (IU/l) | 64–300 | M | 634.6±366.8 | ND | 485.1±406.7 | <0.01 |
| | | F | 320.5±179.4 | ND | 226.7±112.2 | 0.05 |
| TBIL (µmol/l) | 5–21 | M | 123.6±86.5 | 122.5±104.7 | 81.3±105.1 | 0.02 |
| | | F | 68.5±93.4 | 52.5±57.1 | 26.5±19.5 | 0.07 |

AST – aspartate transaminase; ALT – alanine transaminase; GGT – gamma-glutamyl transferase; AP – alkaline phosphatase; TBIL – total bilirubin; M – male; F – female; SD – standard deviation; ND – no data available

**Table 3.** HEV in patients with moderate and severe clinical forms

| Sex | Age (years) | Laboratory findings (mean ± SD) | | | | Clinical history | |
|---|---|---|---|---|---|---|---|
| | | AST (IU/l) | ALT (IU/l) | GGT (IU/l) | TBIL (µmol/l) | Previous and underlying diseases | Severity |
| Female | 30 | 204±209 | 872±932 | 264±251 | 156±59 | Acute HBV-hepatitis | Severe |
| Male | 31 | 238±135 | 643±409 | 2606±1376 | 88±23 | Cholecystectomy, hepatic resection-adenoma | Moderate |
| | 59 | 932±1100 | 2165±1521 | 766±28 | 73±28 | HBV-infection | Moderate |
| | 59 | 475±307 | 894±776 | 374±149 | 75±42 | Diabetes mellitus, CVD | Moderate |
| | 74 | 994±1534 | 1369±1499 | 201±56 | 308±73 | CVD, cholecystitis, fatty liver | Severe |
| | 84 | 442±41 | 258±17 | 176±14 | 356±25 | HCV-infection, ischemic, cerebral insult | Moderate |
| | 84 | 480±538 | 480±502 | 104±55 | 206±109 | Cholecystitis, fatty liver, malaria | Severe |

HBV – hepatitis B virus; HCV – hepatitis C virus; CVD – cardiovascular disease

illness. We supposed that it was Gianotti–Crosti syndrome. During the hospital stay additional clinical presentations developed: headache, edematous syndrome, severe fatigue, and sleepiness. The laboratory results showed disorder of hemostasis with elevated INR – 3.1 (normal range: 0.7–1.3), with prolonged prothrombin time – 22 seconds (up to 14 seconds), low serum albumin – 28 g/l (normal range: 35–52 g/l). The combination of two hepatotropic viruses is a risk factor for suspected severe clinical course. Based on this and the laboratory findings, the case was mentioned as a severe form of acute hepatitis. At six months from the beginning of the illness she was in good health, the liver enzymes were normal, and the serological tests showed seroconversion to anti-HBs and anti-HEV IgG.

The second case was a 74-year-old man, in whom the sickness began with signs of vomiting, nausea, anorexia, abdominal pain. Icteric syndrome gradually developed. Man had a previous medical history for cardiovascular disease and cholecystitis. During the hospital stay jaundice deepened, lethargy and weakness appeared. Laboratory markers found prolonged prothrombin time (22 seconds), high bilirubin (418 μmol/l), and tendency to quick decreasing of liver enzymes. The case was accepted as severe, and supportive treatment for impending liver failure was applied. After adequate therapy the man was discharged with better clinical and laboratory characteristics.

The third case was of an 84-year-old man with acute hepatitis E and cholecystitis on the background of fatty liver and undergoing malaria and underlying heart disease. The beginning of the disease was with high temperature, jaundice, fatigue, edematous features. During the illness edematous symptom developed, pleural effusion, severe fatigue, weakness with drowsiness appeared. Laboratory results marked high bilirubinemia (329 μmol/l), low serum cholinesterase – 2.5 IU/l (normal range: 4.62–11.5 IU/l) and low serum album – 28 g/l (normal range: 35–52 g/l). The case was classified as severe, and supportive treatment was applied. After a prolonged hospital stay, he was discharged with improved laboratory parameters and good clinical condition.

All 20 patients were hospitalized at our department, keeping bed rest and special diets. The average hospital stay per patient was 14 days. The treatment was supportive. In cases of severe form, specific treatment was applied. All 20 patients recovered of HEV infection without complications. No chronic or fatal cases were recorded. During the follow-up period of six months clinical symptoms disappeared and the elevation of liver enzymes and bilirubin level dropped to normal range.

## DISCUSSION

In Bulgaria, like in other industrialized countries, the incidence of HEV infection during the study period of eight years is on the rise [13, 14, 15]. This is the result of the ever improving knowledge on HEV infection as well as the progress in modern diagnostic methods. The cases presented in this report are sporadic and autochthonous such as other non-travel related hepatitis E cases reported previously in the Netherlands, Germany, England and Wales, France, Italy, Serbia, Montenegro, Greece, Romania and Hungary [13, 14, 16-24]. In this study, as in the previously reported cases, the male sex was more affected than the female sex, the mean age was 51 years [21, 25]. Unlike in endemic areas, where HEV infection showed no age prevalence, a higher prevalence was seen among older patients in non-endemic regions [13, 14, 16, 18, 20, 21].

The zoonotic characteristics of the virus were in favor of an infection acquired through a foodborne route. Traditional Bulgarian meat is pork. It's consumed either cooked, dried, as in a raw sausage called "sudjuk", or fried. Bulgarians are accustomed to breeding pigs domestically for home consumption. These animals are slaughtered in winter for food, which could be the reason for the substantial increase of hepatitis E in our study during winter and spring. Bulgarian sausages are made of pork, and intestines are used to rap the sausages containing a mixture of flesh, liver, kidneys, bowels and other animal parts. After that it is dried for some weeks and consumed raw or cooked. Feagins et al. [26] first reported the presence of infectious HEV in pig livers sold at groceries in the USA [26]. Colson et al. [17] reported HEV transmission by eating raw traditional French pig liver sausage "figatellu." Berto et al. [27] reported the presence of infectious HEV in pork liver sausage and its consumption was considered a risk factor for HEV infection. In a study by Borgen et al. [13], 42.1% of the reported cases ate dried pork sausages. Wichmann et al. [14] concluded that the consumption of undercooked raw meat from wild boar, beef, and offal were associated with an autochthonous HEV infection in Germany [14]. In Japan, Kanayama et al. [28] mentioned a transmission of HEV after ingesting inadequately cooked pork. Petrović et al. [25] reported high prevalence of HEV antibodies in general Serbian population. These Serbian researchers supposed zoonotic potential of HEV in their country, associated with traditional food custom of eating barbeque of piglet meat [25]. These conclusions corresponding with high prevalence of anti-HEV IgG among blood donors, pigs and pork products [25]. Bulgarian traditional food customs are too related to our neighbor Serbia. Consequently, we suppose that the foodborne transmission of HEV infection in our study (20 reported cases in one hospital) may be associated with eating of dried sausages or other undercooked pork in cold seasons. In support of this is the epidemiological data on eating pork.

## CONCLUSION

In this study, the main clinical presentations were typical for other acute viral hepatitis. Jaundice, fatigue and hepatomegaly are significant variables in the study ($p<0.01$). The laboratory investigations showed significant increase in the levels of liver enzymes, especially of AST, ALT and AP ($p<0.001$), similar to previously published data [17, 18, 20]. The cytolysis process is well-presented among men and is associated with moderate to severe forms of hepatitis. No correlation between age and liver complica-

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tions was established. The comparison of AST, ALT, GGT, AP, and bilirubin between men and women showed significantly higher values in men than in women. Moderate to severe HEV infections were more common among patients with previous underlying liver disorder. Based to our observations, we presume that aging, male sex and pre-existing disease or co-infection are risk factors for developing severe course of the illness.

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## NOTE

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# Епидемиолошке одлике и клиничке манифестације инфекције хепатитисом Е у Бугарској: извештај о 20 болесника

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**КРАТАК САДРЖАЈ**

**Увод** Хепатитис Е је једна од водећих клиничких манифестација акутног вирусног хепатитиса у земљама у развоју. У индустријски развијеним државама током последњих неколико година повећан је број спорадичних „аутохтоних" случајева инфекције вирусом хепатитиса Е (ХЕВ).

**Циљ рада** Циљ ове студије је био да се анализирају епидемиолошке, клиничке и лабораторијске особине инфекције ХЕВ-ом међу болесницима хоспитализованим на Одељењу за инфективне болести Војномедицинске академије у Софији, у Бугарској.

**Методе рада** Ретроспективна студија је изведена између децембра 2004. и септембра 2012. године на Одељењу за инфективне болести Војномедицинске академије у Софији, а обухватила је 806 случајева акутног вирусног хепатитиса. Етиолошка анализа успостављена је помоћу теста *ELISA*. Статистичка анализа урађена је помоћу програмâ *Excel 2007* (*Microsoft*, Редмонд, Вашингтон, САД) и *SPSS Statistics 19.0* (*IBM Corp.*, Арманк, Њујорк, САД).

**Резултати** Специфична реакција на антитела анти-ХЕВ-*IgM* и анти-ХЕВ-*IgG* уочена је код 20 болесника (2,48%). Најчешћи симптоми били су жутица (код 85% болесника), замор (85%), анорексија (65%), нелагодност у трбуху (55%) и повишена телесна температура (40%). Средња вредност нивоа аспартат-трансаминазе била је 521 *IU/l*, а аланин-трансаминазе 881 *IU/l*. Холестаза је била блага, обележена средњим вредностима гама-глутамил трансферазе од 418 *IU/l*, и алкалне фосфатазе од 486 *IU/l*.

**Закључак** Извештај је обухватио 20 аутохтоних, спорадичних случајева акутне инфекције ХЕВ-ом. Разматрали смо зоонотску етиологија вируса и преношење инфекције храном. Установили смо да су животна доб и постојеће основне болести фактори ризика за тежи ток инфекције овим вирусом.

**Кључне речи:** аутохтона инфекција вирусом хепатитиса Е; клинички ток; биохемијски показатељи

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