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HEPATITIS E VIRUS INFECTION – A NEW THREAT FOR EUROPE

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ABSTRACT

Of 20 million of patients infected with hepatitis E virus (HEV) worldwide 57 thousand dies each year. HEV-infection is not longer regarded as a diseases in developing endemic countries of Asia, Africa and Latin America. The majority of European countries faces increasing number of endemic infections. They are caused by seven different genotypes and be responsible for acute and chronic infections. HEV is of zoonotic origin causing infections in pigs and boars which are a source of infection for humans. Infections occur orally after consumption of infected water or meat. HEV-infection is most dangerous for patients receiving immunosuppressive therapy, infected with HIV, after transplantations of solid organs and elderly. In some patients, including pregnant women, acute HEV has a serious course with fatalities reaching even 25%. Chronic HEV-infection may develop in patients following solid organ transplantations and requires long-term antiviral therapy. HEV-infection is a growing public health problem in Europe, which implies the necessity of routine screening in selected populations, especially immunocompromised.

Key words: *HEV, the native infection in Europe*

INTRODUCTION

Of 20 million of patients infected with hepatitis E virus (HEV) worldwide 57 thousand dies each year (1, 2). For many years HEV was regarded as endemic disease prevalent mainly in developing countries of Asia, Africa and Latin America. Sporadic outbreaks in Europe were noted especially among immigrants from endemic areas. Currently acute and chronic hepatitis E is prevalent worldwide. More and more of HEV-infection cases occur endemically in Germany, Great Britain, France, Hungary and Holland. Among groups with high prevalence of HEV-infections are patients receiving immunosuppressive therapy, especially after solid organ transplantations but also with HIV infection and elderly. Seven biologically distinct genotypes of HEV are known. HEV infects not only human but being typical zoonosis affects pigs and boars (3). Current knowledge on hepatitis E needs to be redefined due to the spreading of HEV-infections in Europe.

ETIOLOGY

Hepatitis E virus belongs to genus *Hepevirus* of Hepeviridae family. HEV is a round, non-enveloped virus with single stranded RNA genome divided into 7 genotypes with further subtypes. The infection in usually transmitted orally, however other possible routs of infection include mother to child transmission or during blood transfusion. HEV in pathogenic for humans but also pigs, boars, deers, mongooses, camels and rabbits. Pigs are considered for the most common reservoir of HEV (4, 5).

HEV virion is of variable size between 27-43mm. Its genome consists of 3 overlapping open-reading frames ORF1, ORF2, ORF3. ORF-1 is coding structural proteins - viral replicase and helicase which are essential for virion assembly. ORF-2 is responsible for synthesis of capsid proteinsand ORF-3 supports ORF-2 and is engaged in processes of virion secretion (2, 4, 5).

PATHOGENESIS

The effect of HEV on infected hepatocytes in largely unclear, mainly due to the lack of efficient in vitro-replication systems. The virus is probably cytopathic, immunocytotoxic but also induces hepatocyte cell death. In liver histopathology of subjects with acute, severe hepatitis E focal necrosis, periportal inflammatory lesions and activation of hepatocyte apoptosis. The most

common cells observed in inflammatory infiltration are neutrophil and CD8 cytotoxic T-cells. The infiltration is accompanied by a marked cholestasis, especially in small bile ducts with coexisting cholangitis. Moreover, in the liver histology the formation of hepaticytic pseudorosettes, gland-like arrangement and gland-like transformation are observed. Interestingly, the liver histology differs between patients with HEV-infection acquired in endemic areas and those infected in Europe. This might suggest an influence of HEV-genotype on liver morphology (6).

EPIDEMIOLOGY OF HEV

Infections with HEV are nowadays a world health problem. Genotypes 1 and 2 occur mainly in developing countries of Asia, Africa and Middle America. The infection is usually acquired with contaminated water (7). HEG genotype 1 and 2 infections are also noted in domestic pigs, which could serve as reservoir and potential source of HEV for humans.

In contrast, HEV genotype 3 is prevalent worldwide including high-income countries. The main reason for infection of HEV genotype 3 is consumption of undercooked pork meat and liver. (8, 9). Domestic pigs and wild boars are a main reservoir of HEV genotype 3. In Latium (Italy) in epidemiologic study HEV genotype 3 was found in 40.7% of boars (10). Acute HEV infections in pregnant woman usually caused by genotype 3, more rare by genotype 1 are the most North India, Pakistan, Somalia, Sudan and Nepal (11).

Infections with genotype 4 HEV are observed worldwide but the most commonly in Asia. They are also common in domestic pigs (12). In 2010 *Colson et al*. described multiple cases of HEV-infection among Italians eating sausages based on wild boar meat (*figatelli*). Extensive molecular studies of those cases allowed for a distinction of 2 new genotypes of HEV: genotype 5 and 6 (8, 13). Genotype 7 of HEV was isolated in camels and its biologic characteristics are similar to genotype 5 and 6 (4).

In Europe domestic infection with HEV were confirmed in United Kingdom, France, Italy, Germany, Hungary, Holland, Belgium, Spain, Sweden and Russia (5). *Borgen et al*. assessed the types of digested meats and direct contact with various animals among Dutch with acute hepatitis E. Subjects included did not travel to endemic areas. Authors did not observed an association between contacts with animals and HEV-infection. On the other hand, the most probable route of infection in this population was consumption of pork (14). It is likely that route of HEV-infections is similar in other European countries.

Currently pig farm workers, veterinarians, subjects having frequent contacts with pigs and boars as well as sewage system workers are considered as a high risk populations. This threat is prevalent worldwide, however infrequent in Europe.

CLINICAL PRESENTATION

The incubation period of HEV-infection is usually between 15 and 60 days but may depend on HEV-genotype and might reach even 6 months in HEV genotype 3 (14). The course of acute hepatitis E varies but is usually mild.

Patients with deficits in immunity as well as receiving immunosuppressive therapy are considered as important groups at risk of HEV-infection. In the study of *Bauer et al*. in 11 of 23 subjects with acute hepatitis E no symptoms were observed. Icteric course was observed in four patients but ALT activity did not exceed 1300 IU/mL, in none of patients coagulopathy was noticed. All patients with icterus acute disease previously received immunosuppressive therapy due to the rheumatoid disorders. None of those patients developed chronic HEV infection (15). In another study held among children receiving immunosuppressive therapy in Russia among 87 patients anti-HEV IgG positivity was detected in 5.7%. Comparative study in healthy children showed seroprevalence rates of 1.4%. In none of children symptomatic acute HEV was noticed (16). In Italy among HIV-infected patients anti-HEV IgG antibodies were detected in 6.7% (34/509). On the other hand, in none of those patients symptoms of acute hepatitis E nor chronic sequels were observed (17). Similar study performed in Greece among HIV-infected individuals shown anti-HEV IgG positivity in 7.3%. Also in this study researched did not observe episodes of acute liver injury (18).

On the other hand the course of acute hepatitis E might be sometimes serious. Retrospective analysis of patients hospitalized in due to the drug induced liver injury in one center in Switzerland revealed that in 3/158 patients HEV-infection was causing liver injury (19). *Boregn at al*. described series of 19 acute hepatitis E cases mainly seniors (age range 50 – 84), in whom the infection was acquired in Holland. The most frequent symptoms included dark urine (84%), jaundice (79%), malaise (73%), stool discoloration, pruritus, nausea, vomiting, fever and abdominal pain. Among those patients male predominance was observed (17/2), (14). In another retrospective study by *Manka et al*. analyzing the cases of severe liver damage in 80 patients in Essen in years 2006-2013 authors reported that the HEV caused liver damage in 10-15% of cases. This conclusion was based on prevalence of anti-HEV

IgG antibodies (15%), IgM (9%) and HEV-RNA (10%), (20). Various observations of acute hepatitis E cases suggest that symptoms mainly develop in patients with compromised immunity, especially man.

In 25-30% of pregnant women acute hepatitis E has a severe course. Fulminant hepatitis leading to liver insufficiency and failure of therapy might develop (21). Acute hepatitis E in pregnant women might affect fetus development and preterm deliveries. Moreover, mortality in newborns from mother suffering from acute hepatitis E was noticed. On the other hand, there are no specific recommendations, especially of pregnancy discontinuation is not recommended (11). Infections with HEV genotypes 1 and 3 are the most common causes of fulminant hepatitis E in pregnant women (22).

More and more often chronic hepatitis E is being diagnosed, especially in patients with immunedeficiencies (1). *Bouts et al*. describe the evolution of chronic hepatitis E in two Western-European children after kidney transplantation. None of them had any symptoms of acute liver injury (23). In a prospective study conducted in Germany among heart recipients of 274 patients 4 were chronically infected with HEV with active liver inflammation and advanced liver disease in some (24). In a recent study in 287 patients after liver transplantation in 4 (1.4%) positive HEV-RNA was detected twice in priod of 6 months suggesting chronic HEV inaction. None of those subjects traveled to endemic areas of HEV-infection. In all subjects the course of chronic hepatitis E was asymptomatic (25). *Kamar et al*. evaluated the prevalence of chronic HEV-infection in patients after organ transplantations who had acute hepatitis E. In this study prevalence was 60%, chronic HEV-ibnfection was associated with tacrolimus, while the reduction of immunosuppressants decreased the prevalence of chronic HEV-infection to 30% (26).

DIAGNOSIS OF HEV INFECTION

Detection of IgM and IgG antibodies against HEV by ELISA method is the first step in diagnosis. The presence of antibodies is not a prove of infection but allows to confirm the contact of immune system with the virus. Detection of anti-HEV IgM and IgA antibodies strongly suggests acute hepatitis E (27). In all patients with anti-HEV antibodies the evaluation of HEV-antigen and HEV-RNA is recommended. Most commonly HEV-RNA is tested with RT-PCR method. The presence of HEV-antigen (HEV-Ag) in serum or stool can be assessed by EIA-method and is easier and cheaper than PCR. On the other hand this test is less sensitive than RT-PCR but more sensitive than nested RT-PCR (28). HEV genotype can be assessed by sequencing of viral genome mainly in region of ORF2, especially in position 148 (14).

TREATMENT

There are no standards of therapy of acute and chronic hepatitis E. Moreover no therapies has been approved by FDA as effective against HEV. *Manka et al*. used ribavirin (RBV) in 5 patients with acute, symptomatic hepatitis E patients which resulted in virus elimination in all cases (20). *Galante et al*. treated 4 patients with chronic HEV-infection with 400-800mg ribavirin for 3 months. This therapy was effective in 3 patients, fourth eliminated HEV after additional course of retherapy (25). Multicenter analysis of RBV efficacy in chronic HEV-infection in patients after organ transplantations shown overall efficacy of 68% (sustained viral response – SVR), (29). Among one of the reasons of lack of response could be recently described G1634R mutation in the hepatitis E virus RNA polymerase (30). *Nan et al*. observed high efficacy of antisense peptide-phosphorodiamidate morpholino oligomers (PPMOS's) against HEV in in-vitro studies. PPMO's inhibit translation of viral genes and were for the first time described as a potential therapy of influenza viruses (22).

Studies on preventive vaccine against HEV are advances. It seems that wide application of vaccine will follow shortly. It's of upmost importance in endemic region for HEV-infections (31, 32).

SUMMARY

HEV-infection is an emerging threat in European counties. More and more often endemic infections are diagnosed. HEV infections, especially chronic are dangerous for patients with impaired immunity. Numerous studies suggest a need of routine screening for hepatitis E among selected populations in Europe.

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