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# Hepatitis E as a novel approaching challenge of endemic infection

## Zapalenie wątroby typu E jako nowe nadchodzące wyzwanie związane z zakażeniem endemicznym

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**Key words**

viral hepatitis, hepatitis E, acute hepatitis, chronic hepatitis, HEV

**Słowa kluczowe**

wirusowe zapalenie wątroby, zapalenie wątroby typu E, ostre zapalenie wątroby, przewlekłe zapalenie wątroby, HEV

Summary

The paper presents basic data on the hepatitis E virus (HEV) and the disease caused by it. Traditionally, hepatitis E is regarded as a problem found in developing countries with hot climates and poor sanitation. Acute hepatitis E poses a high risk to pregnant women. In developed countries, hepatitis E has been diagnosed in people returning from trips to endemic areas. In recent years our knowledge on HEV and hepatitis E has been updated with important practical information.

In this paper attention is drawn to new information on HEV infections: current classification and the genetic diversity of the virus, reports on its presence in industrialized countries as an aetiological factor of locally acquired hepatitis E and the most important routes of infection with the virus. HEV can induce various clinical types of infection, including chronic disease and non-hepatic manifestations. Populations of patients particularly prone to contracting the infection, diagnostic methods for hepatitis E and potential therapeutic options, so far available only in special cases, are presented. Interestingly, a possibility has emerged to efficiently prevent the active disease through immunization with a recombinant antigen (so far only in China).

It is essential for the recognition of HEV infection to include it in the differential diagnosis of diseases with jaundice and/or unexplained hyperaminotransferasemia.

The aim of this paper is to draw the attention of readers to the discussed problem in order to achieve a more detailed insight into the status of HEV infections in Poland.

Streszczenie

W artykule przedstawiono podstawowe dane dotyczące wirusa zapalenia wątroby typu E (HEV) oraz wywoływanej przez niego choroby. Tradycyjnie wirusowe zapalenie wątroby typu E (wzw E) postrzegane jest jako problem występujący w krajach rozwijających się, z gorącym klimatem i niedostatecznymi warunkami sanitarnymi. Ta postać ostrego wzw stanowi duże zagrożenie dla kobiet ciężarnych. W krajach rozwiniętych rozpoznawano chorobę u osób wracających z podróży do obszarów endemicznych. W ostatnich latach nasza wiedza o wirusie oraz wzw E została uzupełniona o istotne praktycznie dane.

W niniejszej pracy zwrócono uwagę na nowe informacje dotyczące zakażeń HEV: aktualną systematykę oraz różnorodność genetyczną wirusa, odnotowano jego występowanie w krajach uprzemysłowionych jako czynnika etiologicznego lokalnie nabytego wzw E oraz podano najważniejsze drogi przenoszenia. Wirus może indukować różne postaci kliniczne zakażenia (w tym proces przewlekły oraz manifestacje pozawątrobowe). Wymieniono populacje pacjentów szczególnie podatne na nabycie zakażenia, zasady rozpoznawania zapalenia wątroby typu E oraz potencjalne możliwości terapeutyczne tej choroby, na razie tylko w wyjątkowych przypadkach. Warto zauważyć pojawienie się możliwości skutecznej profilaktyki czynnej choroby za pomocą szczepień z zastosowaniem rekombinowanego antygenu (na razie tylko w Chinach).

Podstawą do rozpoznania zakażenia HEV jest uwzględnianie go w diagnostyce różnicowej chorób przebiegających z żółtaczką i/lub niewyjaśnioną hiperaminotransferazemią.

Celem artykułu jest zwrócenie uwagi Czytelników na dyskutowany problem, co zaowocuje rozpoznaniem sytuacji dotyczącej zakażeń HEV w Polsce.

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## INTRODUCTION

In his classical system of viral hepatitis, MacCallum distinguished two types of the disease: serum hepatitis and infectious hepatitis (1). In subsequent decades, several primary hepatotropic viruses were identified, which helped to extend MacCallum's classification, following its basic structure, where the major transmission route for infection was the key criterion for classification. According to the extended system, the group of enterically transmitted viruses (mainly via the faecal-oral route) includes hepatitis A and E viruses (HAV and HEV), while the parenterally transmitted viruses include hepatitis B, C and D viruses (HBV, HCV and HDV).

HEV identification was associated with the epidemics of hepatitis of unknown aetiology which occurred among Soviet soldiers stationed in Afghanistan in the 1980s (2). One of the researchers ingested a faecal extract derived from patients. The researcher contracted the disease, and an electron microscope examination of his stools revealed the presence of spheroid virus-like particles of 27 to 30 nm in diameter. The particles reacted with sera from the patients and serum from the researcher taken a few weeks after the infection occurred. It was possible that the new infectious factor was transmitted to other primates (crab-eating macaque, *Macaca fascicularis*), causing similar symptoms in them. The HEV genome was described at the beginning of the following decade (3, 4).

## THE VIRUS

The first virology analyses suggested that this previously unidentified aetiological factor of enterically transmitted non-A, non-B hepatitis was similar to viruses from the Caliciviridae family and for this reason HEV was classified to this group for a certain time. However, because of significant differences in the organisation of the genome, the virus was finally classified to a separate family, *Hepeviridae* (genus *Hepevirus*) (5).

HEV is a small (27-34 nm), spheroid, non-enveloped virus, with icosahedral symmetry, containing a single-strand positive-sense RNA that is approximately 7200 bases in length. The genome is organized in three open reading frames (*ORF1-3*), limited from both ends (5' and 3') with non-coding regions. The product of *ORF1* is a large non-structural polyprotein whose components play a key role in virus replication (e.g. RNA-dependent RNA polymerase activity) (6). *ORF2* encodes the structural protein of the viral capsid, which contains epitopes inducing the formation of neutralizing antibodies (6). Numerous antigens originating from *ORF2* are basic design elements for various serological assays used in the diagnostics of HEV infection. In addition, recombined products of this region have been used for the production of preventive vaccines. The *ORF3* derivative is a small-size phosphoprotein linked with the cytoskeleton and the HEV capsid protein (6). It is thought to optimize the conditions in the host cell by facilitating virus replication, inhibiting the mechanisms of natural immune response, and taking part in the process of HEV leaving the infected cell. ORF3 protein is the key substance determining the *in vivo* infectivity of HEV. HEV replicates in the cytoplasm of the infected host cells.

Although the heterogeneity of HEV strains able to cause the disease in humans is significant (4 genotypes and at least 24 subtypes) (7), all variants represent one serotype of the virus (8). Genotypes 1 and 2 cause infections only in humans and primates, while infections caused by genotypes 3 and 4 also affect certain species of other mammals (domestic swine, wild boar, deer), which can be a source of zoonotic diseases transmitted to humans (9). Anti-HEV and/or HEV-RNA antibodies were found in a wider range of animals (chickens, rabbits, rats, mongooses, ferrets, dogs, cats, goats, cattle, horses and sheep), but it is not known whether this fact has any practical role in the aspect of human disease (10, 11).

## EPIDEMIOLOGY OF HEV INFECTIONS

The genetic diversity of HEV has important practical implications because individual genotypes are characterized by different geographical coverage and a number of epidemiological particulars. In addition, there are differences in the clinical course of individual variants of the viral infections in humans. The strains belonging to genotype 1 are present in the developing countries of Asia and Africa, genotype 2 was found in Mexico, Chad and Nigeria, but genotype 3 has the widest distribution, occurring throughout the world (except Africa). Finally, genotype 4 is found mainly in Asia, but a small number of cases have also been reported from Western Europe (7, 12, 13).

### Highly endemic areas

Until recently HEV infection was believed to be common only in endemic areas of hepatitis E, which included developing countries of the subtropical and tropical zones, characterized by poor socio-economic conditions and sanitation (14). In these areas, HEV causes periodic water-borne outbreaks (associated with the contamination of water with human and animal faeces), but is also the major cause of sporadic cases of acute viral hepatitis in periods between epidemic outbreaks (15). Furthermore, hepatitis E is an important cause of the decompensation of chronic liver diseases in endemic areas (16, 17). Hepatitis E in non-industrialized countries is mainly diagnosed in adolescents and young adults (the age of patients is usually in the range of 15-40 years). For reasons unknown, symptomatic HEV infection is associated with high mortality in pregnant women. The analysis of cases in these areas and cases of disease contracted when travelling to endemic countries, but reported from industrialized countries, led to the conclusion that the infections are mainly caused by HEV genotype 1.

### Low-endemic areas

Epidemiological studies carried out in developed countries in the 1990s demonstrated the presence of

anti-HEV antibodies in 1.1-4.5% of blood donors in the studied populations (USA, Switzerland, the Netherlands) (18-20), but hardly any attention was paid to these findings (21). After 2000, numerous papers were published describing sporadic cases of hepatitis E in industrialized areas in residents who had not travelled to endemic regions (22-28).

Moreover, the analysis of HEV seroprevalence conducted in the last few years using new serological tests (offering greater diagnostic accuracy) has confirmed the more frequent presence of anti-HEV IgG in different populations from developed countries than in previous studies, supporting the observation that HEV infections are present there as an endemic problem. For example, HEV seroprevalence data for blood donors were as follows: 3.7% in Japan (29), 4.2% in New Zealand (25), 4.9% in Switzerland (30), 5% in Italy (Rome) (31), 16.2% in England (32), 16.8% in Germany (33), 18.3% in the United States (34), 20.6% in Denmark (35), and 52.5% in the south-west of France (36). Endemic hepatitis E in industrialized countries is typically associated with sporadic infections caused by genotype 3 HEV and rarely genotype 4 (12, 13, 37). As indicated earlier, both variants of the virus also cause infections in other mammals. Therefore, it is believed that in the areas where these variants of the virus occur, HEV transmission is related to the animal reservoir. The sources of infection considered to be the most common include the consumption of raw or undercooked meat (38) and seafood (39), and direct contact with animals (34). Cases of disease are reported with significantly higher frequency in middle-aged and old-aged men, and additional risk factors include alcohol consumption and chronic liver disease (37, 40-43).

## CLINICAL PICTURE OF HEV INFECTIONS

The clinical picture of HEV infection is highly diversified, and includes completely asymptomatic (subclinical) course, acute hepatitis with jaundice (of these about 20% of patients have cholestasis in the course), and life-threatening acute liver failure (44). Clinical symptoms of acute hepatitis E do not differ from those in diseases caused by other primary hepatotropic viruses. Mortality associated with the disease during an epidemic in endemic areas is 0.5-4% (44). As mentioned previously, mortality is particularly high (up to 31%) in pregnant women, especially in the 3rd trimester of pregnancy (45-47). In some studies analyzing sporadic cases of the disease in this group of patients in India, the reported mortality was in the range of 51-66% (48, 49). Autochthonous hepatitis E in developed countries is not associated with such a risk.

The discrepancy between the prevalence of antibodies suggesting exposure to HEV infection (sometimes significant) and the number of recorded cases of hepatitis E (significantly lower) observed in epidemiological studies indicates that the majority of these infections are asymptomatic. These findings are confirmed by data obtained during the analysis of a hepatitis E outbreak on a ship during a voyage around the world (67% of asymptomatic HEV infections) (39) and a very high rate of asymptomatic seroconversion (over 98%) in a large study in China (50).

Until recently hepatitis E was thought to be manifested only as an acute HEV infection. Although there were single case reports suggesting the possibility of a chronic infection with the virus (51, 52), only Kamar et al. (53) were the first ones to notice the existence of the problem of chronic hepatitis E in a population of patients after solid organ transplants. Later it was found that chronic HEV infection can also occur in other groups of immunocompromised patients (54, 55). All cases reported to date have been associated with infection caused by genotype 3 HEV.

In terms of the clinical picture of HEV infection, it is also worth noting that extrahepatic symptoms can coexist in the course of hepatitis E. Of these symptoms, neurological syndromes (56, 57), hematologic abnormalities (58, 59), pancreatitis (60), severe myositis (61) and glomerulonephritis with or without cryoglobulinaemia (62, 63) have been reported.

## DIAGNOSIS

An important role in the diagnosis of HEV infection is attributed to the detection of antibodies against different antigens of the virus, usually using immunoassays. IgM antibodies usually appear in a short time (in the majority of patients they are found within two weeks of the onset of clinical symptoms) and are typically sustained for several months. The anti-HEV IgGs are usually detected shortly after IgM, and their presence can often be confirmed over the next few to over ten years, although their rapid decline has also been reported (64). Anti-HEV IgGs are most often used in practice as a proof of exposure to HEV. The most serious problem in serological diagnostics is that the accuracy of serological tests can vary significantly (32, 36, 64).

HEV infection is clearly confirmed by the detection of the viral genome in biological material obtained from the patient (usually blood or stool). It is particularly important in the diagnostic process in immunocompromised patients with impaired serologic response and thus unable to produce suitable antibodies in response to infection. Molecular diagnostic tests are also crucial for further evaluation of response to antiviral treatment.

Recently a standard variant of the HEV genome was developed for diagnostic purposes (65). Unfortunately, HEV-RNA is detectable in the diagnostic material obtained from the patient for a limited and relatively short time (for about 2 weeks after the onset of clinical symptomsin the blood and additionally for the next 2 weeks in the stool of patients with acute hepatitis E) (50).

## TREATMENT OPTIONS

Symptomatic HEV infection usually has a self-limited course and ends with the patient's recovery. There are no drugs approved for the treatment of hepatitis

E. However, the experimental use of ribavirin and/or different interferon alpha formulations was reported in special cases. These included: severe acute HEV infection (66) and hepatitis E in recipients of solid organs (67-70), haematological patients (71, 72) and HIV-infected patients with significant impairment of immunity (56, 73). Treatment was successful and the sustained disappearance of HEV-RNA was achieved in the majority of patients.

## PREVENTION

In developing countries, access to clean drinking water and compliance with the general rules of hygiene are most important. Because of the existing animal reservoir and the fact that the consumption of infected products of animal origin may be associated with the exposure to HEV, the risk of infection can be reduced by suitable heat treatment of meat dishes. In addition, it is reasonable to avoid the consumption of seafood.

Preliminary animal studies were carried out on several hepatitis E vaccines (74). Finally, two recombinant vaccines for human use were evaluated. They contained the following antigens: a 56 kDa protein, composed of 496 amino acids (derived from the baculovirus expression system) (75), and a 26 kDa protein, composed of 239 amino acids (HEV 239; *E. coli* expression system) (76). The high efficacy and safety of these vaccines has been confirmed. The second of these vaccines, marketed as Hecolin, was finally approved and has been available in China since 2012 (77). It is worth noting that Hecolin ensured protection to all persons who have received three doses of the vaccine.

## CONCLUSIONS

HEV infections may occur in industrialized countries also in people who have not travelled to areas typically considered to be endemic. The clinical course of HEV may include a full range of manifestations – from completely asymptomatic to acute liver failure. In addition, immunocompromised patients can present with chronic hepatitis E. Taking into consideration locally acquired hepatitis E in the diagnosis of patients with elevated transaminase activities is essential for the recognition of this disease.

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received/otrzymano: 10.09.2014
accepted/zaakceptowano: 14.10.2014