VIA MEDICA

CASE REPORT

Int Marit Health
2022; 73, 2: 77–82
10.5603/IMH.2022.0012
www.intmarhealth.pl

ISSN 1641-9251
eISSN 2081-3252

Reactivation of hepatitis B virus infection in a seafarer: an omitted problem of maritime medicine

Michał Rokicki[1], Katarzyna Sikorska[2, 3], Małgorzata Sulima[2], Marta Gesing[1, 4]

[1]University Centre of Maritime and Tropical Medicine, Gdynia, Poland
[2]Department of Tropical and Parasitic Diseases, Institute of Maritime and Tropical Medicine, Faculty of Health Sciences, Medical University of Gdansk, Gdynia, Poland
[3]Department of Tropical Medicine and Epidemiology, Institute of Maritime and Tropical Medicine, Faculty of Health Sciences, Medical University of Gdansk, Gdynia, Poland
[4]Department of Infectious Diseases, Medical University of Gdansk, Poland

ABSTRACT

Infection with hepatitis B virus (HBV), despite the implementation of extensive preventive measures, has remained one of the biggest health problems worldwide. There are still people not covered by the compulsory vaccination programme and carriers of an actively replicating virus among professionally active seafarers. The article is based on a case report of a seafarer with life-threatening reactivation of long-term uncontrolled HBV infection that resulted in decompensated cirrhosis and liver transplant. The case shows clinical aspects of chronic hepatitis B and contributes to discussion about HBV infection with regard to seafarers. The article also analyses the current legal regulations and guidelines in terms of preventing new infections and detecting people already infected with HBV. Considering the specific nature of work on seagoing ships, it is justified to recognise the seafaring as a profession with a high risk of HBV infection. Monitoring the course of the disease can prevent reactivation of inflammatory process and serious consequences of chronic hepatitis B during a cruise. The elementary issue is specific prophylaxis, that is, covering the unvaccinated persons with the vaccination programme. The prevalence of HBV infection and the specifics of the seafarer labour market require development of new international regulations, which will unify Pre-Employment Medical Examination (PEME) protocols and take into consideration compulsory vaccination.

(Int Marit Health 2022; 73, 2: 77–82)

Key words: hepatitis B, seafarers, chronic hepatitis, hepatitis reactivation, maritime medicine, epidemiology, vaccination

INTRODUCTION

Infection with hepatitis B virus (HBV), despite the implementation of extensive preventive measures, including immunisation, has remained one of the greatest global public health problems for decades [1, 2]. Although the epidemiological situation worldwide has improved significantly, there are still people not covered by the compulsory vaccination programme and carriers of an actively replicating virus among professionally active seafarers. This creates the problem of providing these people with necessary, appropriate care, regular monitoring the course of the disease, qualifying for antiviral treatment and assessing their fitness for work on sea-going ships.

Chronic hepatitis B (CHB) develops in about 5% of adult patients infected with the virus, and many of them do not develop acute hepatitis [1, 3]. A characteristic feature of the disease is its phases which reflect the changing relationships between the immune system and the virus [4]. This is expressed by the presence or absence of HBV antigens (HBsAg, HBeAg–), specific antibodies and fluctuations of

✉ Michał Rokicki, MD, Department of Tropical and Parasitic Diseases in Gdynia, University Centre for Maritime and Tropical Medicine, Medical University of Gdansk, Powstania Styczniowego 9B, 81–519 Gdynia, Poland, e-mail: michal.rokicki@hotmail.com

HBV viral load. In individual periods, the degree of inflammation activity varies from the high replication phase with high viral load to latent infection in which HBV-DNA is practically undetectable. The situation in which the virus replicates again and the concentration of HBV-DNA increases significantly is called reactivation [3, 4]. Recurrence of viral replication may finally result in significant, clinical deterioration of liver function. Chronic HBV infection is frequently asymptomatic for many years or produces mild, non-specific symptoms, such as fatigue or depressed mood. In chronic active hepatitis necroinflammatory changes in liver parenchyma with progressive liver fibrosis lead to the development of irreversible liver cirrhosis, which in many cases is the first clinical manifestation of the disease. Another consequence of chronic HBV infection is the increased risk of hepatocellular carcinoma, which remains greater than in the general population even after successful treatment [1, 3–5].

Nowadays, antiviral therapy is available for CHB patients and the eligibility criteria for treatment are strictly defined. CHB infections can be treated with interferon alpha (IFNα, currently pegylated — PegIFNα) or nucleos(t)ide analogues (NAs) such as entecavir or tenofovir. Antiviral agents suppress HBV replication and, consequently, they can slow the liver fibrosis, reduce incidence of hepatocelullar carcinoma and improve long term survival. Although effective treatment may protect against serious complications of CHB, complete eradication of the HBV is not possible. The virus remains in the hepatocytes in the episomal form of DNA — covalently closed circular DNA (cccDNA), which can in some circumstances cause HBV reactivation (HBVr) [4–6]. Below we present a case report of a seafarer with HBVr who developed liver failure requiring liver transplantation.

CASE REPORT

A 61-year-old man was admitted to the Department of Tropical and Parasitic Diseases due to the exacerbation of CHB. The patient was a professionally active chief officer working on cargo ships. He did not report any past medical history except HBV infection. He consumed alcohol occasionally and had never taken immunosuppressant for any reason. HBV infection (HBsAg+) was diagnosed about 40 years earlier, but the patient was not under medical care despite the diagnosis. He has never been referred to an outpatient infectious diseases clinic for further observation and treatment. No clinical assessment of indications to perform more detailed laboratory and imaging examinations was performed. For several months, a gradual deterioration in the patient's health and elevated activities of alanine aminotransferase (ALT) were observed, with a marked increase 2 months before admission to hospital (ALT 1128 U/L). Based on medical history no factor has been identified as a trigger for this increase.

On admission, the patient was in a fair general condition. He complained of weakness and easy fatigue, flatulence, and lack of appetite. The physical examination revealed intense yellowing of the skin and sclera; the abdomen was soft and distended, the liver was not palpable; there were no signs of shock or peritonitis. The patient was confirmed to be infected with HBV; high viral load was found — HBV DNA 2.87×10^6 IU/mL. The infections with other hepatotropic viruses such as: hepatitis A, hepatitis C, hepatitis D, cytomegalovirus, Epstein-Barre virus and human immunodeficiency virus were excluded as well as toxic damage to the liver. The results of other laboratory tests are presented in Table 1.

The abdominal ultrasound showed a liver of normal size and echogenicity, a contracted gallbladder containing a stone of about 10 mm, a non-dilated common bile duct and intrahepatic bile ducts, a homogeneous, enlarged spleen of 127 mm in length, and enlarged prostate gland. No other abnormalities were found.

The patient was treated symptomatically and, after exclusion of any HBV drug resistance, antiviral therapy with Entecavir was initiated. As a result, a decrease in the activity of transaminases was observed, with a persistently high concentration of bilirubin and an increase in prothrombin time given in international normalized ratio (INR) — data are presented in Figure 1.

Despite the treatment, the patient's condition deteriorated. Significant weakness, loss of appetite, itching of the skin and jaundice persisted. Additionally, there were symptoms of haemorrhagic diathesis (nosebleed, bleeding into the right conjunctival sac) and ascites. The patient remained in full verbal and logical contact, but reported problems related to sleepiness and flapping tremors.

Additional studies included:

- In abdominal computed tomography scan, the liver was not enlarged, hypodense, with relatively larger left and caudate lobes — monitoring for cirrhosis indicated. There was free fluid in the peritoneal cavity — perihepatic fluid; however, due to a small amount of fluid between intestinal loops and in the pelvis minor its aspiration for laboratory examinations was not possible. The spleen was enlarged 155 × 55 × 73 mm; two additional spleens were observed. In addition, a small amount of fluid was found in the pleural cavities;
- Doppler ultrasound showed a slightly higher hepatic artery resistance index, without any abnormalities in hepatic blood flow;
- Gastroscopy revealed signs of erythematous gastropathy.

In the following days of hospitalisation, there was an increase in ascites with hyponatremia 124 mmol/L, deterioration of kidney function with an increase in creatinine concentration to 1.34 mg/dL. Due to the increasing pa-

Table 1. Laboratory test results at admission

Parameter	Results	Normal range
Alanine aminotransferase (ALT)	261 U/L	< 45 U/L
Aspartic aminotransferase (AST)	333 U/L	< 35 U/L
Ammonia	53 µmol/L	18–72 µmol/L
α-fetoprotein (AFP)	128.37 IU/mL	0–7.29 IU/mL
Total bilirubin	32.1 mg/dL	0.3–1.2 mg/dL
Alkaline phosphatase (ALP)	145 U/L	40–150 U/L
γ-glutamyltransferase (GGT)	133 U/L	11–59 U/L
International normalized ratio (INR)	1.36	0.8–1.2
Creatinine	0.71 mg/dL	0.6–1.3 mg/dL
Haemoglobin (Hg)	12.4 g/dL	14–18 g/dL
Leukocytes	9.41 G/L	4–10 G/L
Platelets (PLT)	262 G/L	150–450 G/L
Albumin	28 g/L	32–46 g/L
Fasting glucose	100 mg/dL	77–99 mg/dL
Natrium	133 mmol/L	136–145 mmol/L
Kalium	4.1 mmol/L	3.5–5.1 mmol/L

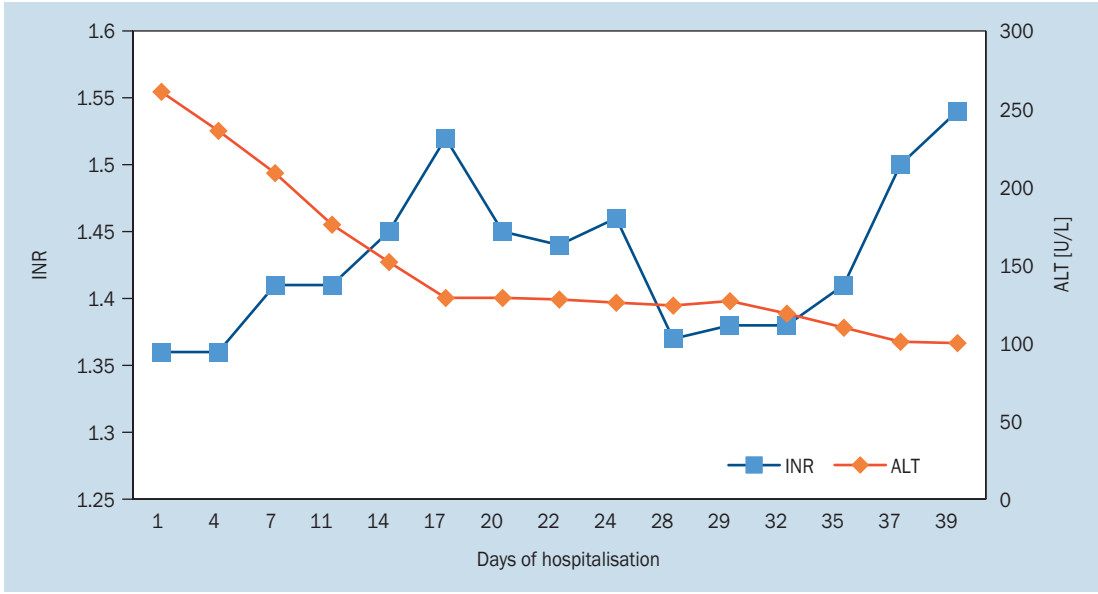

Figure 1. Changes in alanine aminotransferase (ALT) and international normalized ratio (INR) levels during hospitalisation

rameters of inflammation, antibiotic therapy was used. Selected results of the tests at the end of hospitalisation are presented in Table 2.

In follow-up examinations, a significant reduction in viral load (HBV DNA 589 IU/mL) was observed. The assessment of drug resistance using HBV DNA assay showed that the HBV strain was fully susceptible to antiviral drugs. The patient's MELD score was 32. After 6 weeks the patient was transferred to the Department of Liver and Internal Medicine Unit, Department of General, Transplant and Liver Surgery in Warsaw where he was qualified to liver transplantation and underwent this procedure successfully.

Currently the patient remains under the care of the liver transplant and infectious diseases outpatient clinics on

Table 2. Selected results of laboratory tests at 5 weeks of hospitalization

Parameter	Results	Normal range
Alanine aminotransferase (ALT)	101 U/L	< 45 U/L
Aspartic aminotransferase (AST)	178 U/L	< 35 U/L
Ammonia	39.6 µmol/L	18–72 µmol/L
α-fetoprotein (AFP)	8.82 IU/mL	0–7.29 IU/mL
Total bilirubin	26.43 mg/dL	0.3–1.2 mg/dL
Alkaline phosphatase (ALP)	166 U/L	40–150 U/L
γ-glutamyl transferase (GGT)	89 U/L	11–59 U/L
International normalized ratio (INR)	1.54	0.8–1.2
Creatinine	1.44 mg/dL	0.6–1.3 mg/dL
Haemoglobin (Hg)	10.4 g/dL	14–18 g/dL
Leukocytes	14.4 G/L	4–10 G/L
Platelets (PLT)	150 G/L	150–450 G/L
Albumin	25 g/L	32–46 g/L
Fasting glucose	90 mg/dL	77–99 mg/dL
Natrium	125 mmol/L	136–145 mmol/L
Kalium	4 mmol/L	3.5–5.1 mmol/L

continuous, fully effective antiviral treatment with entecavir and his clinical condition is stable and good.

DISCUSSION

It is estimated that over 240 million people worldwide are chronically infected with HBV, with the highest prevalence of infection in low socioeconomic countries, i.e. Southeast Asia, Western Pacific Region and Africa, where the percentage of infected people in the general adult population reaches 6.2% [1, 2, 4]. Globally, viral hepatitis led to 1.34 million deaths in 2015, most of them (96%) were caused by untreated long-term complications, such as cirrhosis (720,000 deaths) and hepatocellular carcinoma (470,000 deaths) [1–5]. This number was comparable with the number of deaths from tuberculosis and higher than those caused by HIV. Worrying is the fact that, while the mortality due to tuberculosis and HIV is declining, the mortality of viral hepatitis is still increasing over the years [1, 2]. The cited data shows that hepatitis B infection remains one of the biggest health problems worldwide.

Data on work on seagoing vessels indicate an increased risk of HBV infection among seafarers who are employed in regions with high prevalence of the virus. Moreover, the increase in risk is not only associated with being ashore, but may also result from the specificity of this profession and the employment structure on board the ship. Sea shipping is an industry of global nature, and the ship-owners, driven by low employment costs, are looking for workers in the most remote parts of the world [7, 8]. Statistics show that the seafarers' labour market is dominated by Filipinos, who constitute up to 80% of all employees [7, 8]. Interestingly, the Philippines is the country with one of the highest rates of HBV infections in the world, where 16.7% of the general adult population are HBsAg positive, which corresponds to 7.4 million chronically infected people [9].

Working on seagoing vessels is related with exposure to extremely parlous conditions. Despite advances in injury prevention in recent decades, seafaring remains one of the most dangerous occupations over the world, which could lead to occupational accidents, such as injuries, falling, being struck by heavy seas on deck [10, 11]. Taking into account significant infectivity of HBV, hazardous working conditions and potential risk of contact with blood seafarers should be qualified as a profession at high risk of exposure to HBV infection. This means that relevant regulations and procedures are required in Pre-Employment Medical Examination (PEME) [12] including detection of infected people and specific prevention of new cases, as well as post-exposure prophylaxis on board.

Protocols for PEMEs developed by national maritime organizations or private shipping companies are based on guidelines published by the International Labour Organization (ILO) and the International Maritime Organization (IMO) [12, 13]. ILO/IMO guidelines do not recommend any routine laboratory tests for seafarers, although they are widely used in practice [12, 13]. This shows the need of finding consensus between organizations and local authorities for unified PEME protocol. The problem of detection and

prevention HBV infection should not be omitted in such a discussion. Nevertheless, most of the seafarers come from developing countries with high prevalence of HBV (e.g. China, the Philippines, Indonesia, the Russian Federation, Ukraine) [2, 7]. What is more, ILO/IMO guidelines do not mention any obligatory vaccinations for seafarers [13]. Considering the nature of the work on the seagoing ships and epidemiology of HBV and other infectious diseases, it seems to be serious oversight.

The epidemiological situation of hepatitis B has been systematically improving for many years. As a result of the introduction of the universal immunisation programmes from 1980s to the early 2000s and the improvement of the standards of medical procedures, the number of cases and the incidence of hepatitis B decreased significantly [2, 14]. The Word Health Organization (WHO) recommends vaccination against HBV for all infants within 24-hours after birth, followed by 2 or 3 doses to complete the series. According to latest WHO estimates, in 2019 coverage of three doses reached 85% worldwide and the proportion of children under 5 years of age chronically infected with HBV dropped down under 1% from around 5% in the pre-vaccine era [2, 14]. Universal hepatitis B immunisation programmes that target infants, with the first dose at birth, have been highly effective in reducing the incidence and prevalence of hepatitis B in many endemic countries. However, these programmes will not have an impact on HBV-related deaths until several decades after their introduction [14].

The WHO recommends vaccination against hepatitis B to people who are particularly vulnerable to infection, but does not list seafarers working on seagoing vessels in this group, as is the case with health care workers [2, 14]. As indicated by analyses of epidemiological data, specific prophylaxis and an increase in the percentage of vaccinated people result in a significant reduction in HBV infections [15]. This confirms the need to vaccinate the population of seafarers who were not covered by the universal hepatitis B immunisation programmes. Here is the role of the doctors assessing seafarer's fitness for work at sea, who should advise vaccinations for workers including not only hepatitis B, but also other vaccinations recommended for travellers. It seems to be justified that the provision on compulsory vaccination should be included in ILO/IMO guidelines and in the national relevant regulation on health conditions required from seafarers.

Chronic hepatitis B reactivation occurs most often in the course of immunosuppressive therapy, biological therapy or antitumor chemotherapy; however, spontaneous reactivation without any apparent reason is also possible [3] — as in the case described above. Given the lack of specific symptoms indicative of active HBV replication, it is possible that inflammation may reactivate during a deep-sea voyage. As the example of our patient shows, the development of full-blown liver failure may occur in a relatively short time. Seafarers often work on seagoing ships for many months, also in hazardous places, without access to qualified healthcare. This poses a risk of reactivation of hepatitis B and the development of liver failure during the cruise without the possibility of obtaining adequate medical intervention.

The serious consequences of hepatitis B indicate the importance of the diagnosis and treatment of HBV infection. The confirmed presence of the HBsAg surface antigen is the basis in the diagnosis of infection, but it should be remembered that in the case of seroconversion in the HBs system, the antigen may be undetectable [1, 4, 16]. Therefore, additional determination of anti-HBc antibodies is justified, thanks to which we are able to identify people with the so-called latent HBV infection, also prone to reactivation of the inflammatory process. It should be remembered that hepatitis B vaccination in this group of patients is not effective and it does not prevent from HBVr [1, 4, 15]. It is also important to avoid the term "chronic carrier" when referring to people infected CHB, since it may cause misconception that latent HBV infection has no serious consequences. Recent studies have focused on the new biomarkers, such a HBV core-related antigen (HBcrAg), which can be helpful in identifying patients with transcriptionally active cccDNA [16]. In the near future it may be a very useful tool in identifying people especially prone to HBVr. Moreover, the detection of HBV-DNA levels has become a fundamental practice for establishing the extent of viral replication and guiding the start of therapy [16].

CONCLUSIONS

Taking into account the specific nature of work on seagoing ships, it is justified to recognize the seafaring as a profession with a high risk of HBV infection. This statement should be followed by activities aimed at preventing new infections, detecting people already infected in order to qualify them for potential antiviral treatment. Monitoring the course of the disease can prevent reactivation of inflammatory process and serious consequences of the chronic hepatitis B during a cruise. The lack of this type of action has led to liver failure and transplantation in the seafarer described in the case report. The fundamental issue is specific prophylaxis that is, covering the unvaccinated persons with the vaccination programme. At the same time, one should not forget about the remaining vaccinations recommended for travellers, which are also recommended for seafarers. That is why it is so important to be aware of this problem among doctors issuing seafarer medical certificates. The prevalence of HBV infection and the specifics of the seafarer labour market should induce international maritime intuitions to develop new regulations for the employment of seafarers,

which will be unified and take into consideration compulsory vaccination.

Conflict of interest: None declared

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