**BRIEF REPORT**

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# THE ELEVATION OF LIVER ENZYMES DUE TO HEPATITIS B VACCINE

*Yusuf Önlen[1], Lütfü Savaş[2], Burçin Özer[3], Nur Efe İris[3]*

Mustafa Kemal University Faculty of Medicine, Departments of Infectious Diseases[1] and Microbiology[2], Hatay, Okmeydanı Training Hospital, [3] Department of Infectious Diseases, Istanbul, Turkey

Hepatitis B virus infection described as the second carcinogen factor after smoking by the World Health Organization (WHO) is a global public health problem (1). It was reported that 15-40% of HBV infected patients would develop cirrhosis, liver failure, or hepatocellular carcinoma and 500 000 to 1.2 million people die of HBV infection annually (2). Because of the high HBV-related morbidity and mortality, the global disease burden of HB is substantial. Hepatitis B viral infection is a preventable disease. Three main strategies have been approved to be effective in preventing HBV infection. They are behavior modification, passive immunoprophylaxis, and active immunization. The implementation of mass HBV immunization program is recommended by the WHO since 1991 (3). Prevention of primary infection by vaccination is an important strategy to decrease the risk of chronic HBV infection and its subsequent complications (4). The serious adverse effects due to hepatitis B vaccine in adults, rarely in children, were reported since 1980's after common usage of hepatitis B vaccine (5). The liver dysfunction, acute exacerbation of autoimmune hepatitis and acute hepatitis B infection after vaccination were reported before (6,7). We wish to report on a young male patient, who presented with enzyme elevation after receiving recombinant-DNA yeast-derived hepatitis B vaccine.

A 27-year-old man referred to the department of infectious disease of Mustafa Kemal University Hospital with the complaints of fatigue, malaise, lethargy and lack of appetite continued for approximately one month. He was research fellow at the university. The past medical history of the patient was unremarkable and jaundice or abnormal liver function tests were previously unknown. He denied any alcohol intake or drug use, and had not been exposed to any blood products. He also had no previous history of chronic disease, surgical operation and close contact with a hepatitis patient. The patient did not take any other potentially hepatotoxic drugs during that period. The patient reported no color change of stool and urine. He reported that he received the first dose of recombinant-DNA yeast-derived hepatitis B vaccine (Gen Hevac B, Aventis Pasteur, France) one month ago after he learned that his wife was hepatitis B carrier and received second dose of the vaccine one day before applying to our clinic.

A physical examination disclosed no remarkable findings. All the systems examinations were normal. Complete blood cell counts were all within the normal ranges. The levels of alanine aminotransferase(ALT) and aspartat aminotransferase (AST) were elevated 90 IU/L (normal: 14-54 IU/L) and 35 IU/L (normal: 15-41 IU/L) respectively and Anti HBs was negative. Serological markers for HBV (HBsAg, anti HBc IgM, anti HBc IgG, HBeAg, anti HBe, and anti-HBs) infection, anti HCV, anti-HAV IgM, anti-HEV, anti-CMV IgM, anti-Toxo Ig M, anti-Toxo IgG, anti-Rubella Ig M, EBV, VCA and anti-HIV were negative and anti-HAV total, anti-Rubella IgG and anti-CMV IgG were positive. Anti HCV was found negative in all subsequent examinations. Anti nuclear and, anti mitochondrial antibodies were negative. Immunglobulin G, A, M and E were in the normal ranges. VDRL, Widal tube agglutination test and serum agglutination test for Brucella were negative. Abdominal

*Correspondence: Dr. Yusuf Onlen*
*Mustafa Kemal University, Medical Faculty, Department of Infectious Diseases and Clinical Microbiology, 31100 Hatay/Turkey*
*Fax:903262144977, Tel: 903262140649*
*E-mail: onlenyusuf@yahoo.com*

**Table 1. The complaints, doses of the vaccine and levels of enzymes on the days of the patient's follow-up**

| Before presenting to infectious diseases clinic of our hospital | | | | |
|---|---|---|---|---|
| ***Follow-up*** | ***Complaints and Hepatitis B vaccine*** | ***ALT**** | ***AST***** | ***Anti HBs*** |
| 30 days ago | First dose of Hepatitis B vaccine<br>No complaints | NT[#] | NT | 0 |
| 27 days ago | Fatigue, malaise, lethargy and lack of appetite | NT | NT | NT |
| 1 day ago | Second dose of Hepatitis B vaccine<br>Fatigue, malaise, lethargy and lack of appetite | NT | NT | NT |
| ***After presenting to infectious diseases clinic of our hospital*** | | | | |
| 1st day | Fatigue, malaise, lethargy and lack of appetite<br>***Third dose of Hepatitis B vaccine*** | 90 | 35 | 0 |
| 30th day | Fatigue, malaise and lethargy, increasing appetite | NT | NT | NT |
| 35th day | Decreasing in fatigue, malaise and lethargy, increasing appetite | 191 | 69 | 0 |
| 60th day | No complaints | 53 | 47 | 41 |
| 90th day | No complaints | 65 | 26 | 94 |
| 150th day | No complaints | 62 | 31 | NT |
| 240th day | No complaints | 26 | 24 | NT |
| First year | No complaints | 58 | 35 | 155 |

*[#]NT: Not tested, *Normal ranges of ALT (alanine aminotransferase); 17-63 IU/L, **Normal ranges of AST(aspartat aminotransferase); 15-41 IU/L*

ultrasound showed that the dimension and parenchyma of the liver were normal. Blood chemistry tests revealed 203 mg/dL total cholesterol (normal: 50-200), 71 mg/dL HDL cholesterol (normal: 29-71). Serum levels of total bilirubin, glucose, total protein, albumin, globulin, LDH, amylase prothrombin time, free T3, free T4, TSH, total iron binding capacity, serum ferritin, and ceruloplasmine were all in the normal ranges. The erythrocyte sedimentation rate was in normal ranges in 30 minutes and in the first hour. Thus all the etiologic factors were evaluated and the diagnosis was determined as toxic hepatitis due to the hepatitis B vaccine. The patient was managed ambulatorily with dietary recommendations for cholesterol elevation and avoiding physical activation.

A month after the first visit of our clinic his complaints were not resolved and he received a third dose of Hepatitis B vaccine. The levels of ALT and AST were not tested in this visit. 35 days after the first visit (five days after 3th dose of hepatitis B vaccination), his complaints were less than the first visit but his appetite increased, the ALT and AST levels were elevated to 191 IU/L and 69 IU/L respectively, and the anti HBs was negative. On the 60th day the patient mentioned that his complaints were resolved and he had no complaints, the levels of ALT and AST were 53 IU/L and 47 IU/L respectively, and the level of Anti HBs was positive (41 IU/L). On the 90th day the level of ALT was 65 IU/L and AST was found 26 IU/L. On the 150th day ALT and AST levels were 62 IU/L and 31 IU/L respectively. Blood chemistry tests except cholesterol and triglyceride were in normal ranges. On the 240th day ALT and AST levels were decreased to 26 and 24 respectively. One year after his first admittance to our clinic, levels of ALT and AST were found 58 IU/L and 35 IU/L respectively and the level of anti HBs was determined positive (155 IU/L). Thus he didn't receveid fourth dose of hepatitis B vaccine. The other parameters were normal after one year. His complaints, the doses of the vaccine and the enzyme levels on the days of the paient's follow up, were shown in Table 1.

Although there are a lot of alternatives referred for being protected against the diseases, the vaccination is the most effective, safe and inexpensive method. Hepatitis B vaccines are of two types, plasma derived and recombinant (8). Recombinant vaccines are produced by cloning the gene encoding HBsAg into yeast cells. The medical and scientific communities have generally accepted that recombinant hepatitis B vaccine a highly purified, genetically engineered, single antigen vaccine is a safe vaccine. Information is presented showing that hepatitis B vaccine contains yeast, aluminum, thimerosal and hepatitis B surface antigen epitopes. There is little doubt that the benefits of the vaccine

overall for outweigh its risks (9).

Pain at the infection site and a temperature greater than 37.3 ºC has been among the most frequently reported side effects. And these side effects don't need to be treated (8). The Hepatitis B vaccine was reported to have acute reactions (i.e. anaphylaxis and urticeria) and dermatological, hematological, vascular, neurological and, ophthalmologic side effects (5).

ALT and AST are used as the determinants for the liver diseases. Especially ALT is the most reliable biochemical value to show the injury of hepatocytes. In the low level of damage to hepatocytes the level of ALT which are dense in the liver cell cytozole, increases more than AST. If the injury of the hepatocytes is serious and there is necrosis, AST level is more than ALT (10)

In the vaccine prospectus, the vaccine is reported to be responsible for the elevation of the liver enzymes (11). The elevation of ALT and AST due to hepatitis B vaccination is rarely reported in literature; Lilic et al reported liver dysfunction and DNA antibodies after hepatitis B vaccination (6). Distinctly our patient didn't have a history of jaundice and the levels of bilirubin, alkaline phosphatase and γ–glutamyl-transpeptidase were in normal ranges. Csepregi reported acute exacerbation of autoimmune hepatitis induced by Twinrix included inactivated HAV and recombinant surface antigen of the HBV (rHBsAg) (12). Post marketing studies occasionally described jaundice and acute hepatitis after the use of Havrix and abnormal liver function tests using Engerix-B (13). HBV vaccination appears to be very effective, and only a few cases of acute hepatitis B infection after vaccination have been reported (14,15).

Moreover, vaccination was never reported to lead to chronic liver disease. The recombinant-DNA yeast-derived hepatitis B vaccine are not known to be hepatotoxins, therefore, an intrinsic hepatotoxic effect is highly unlikely. Rather, they probably caused an idiosyncratic reaction, i.e. hypersensitivity. In the toxic hepatitis related to the drugs, it can be appeared as direct toxic effect, idiosyncrasy or cholestatic reaction (16). In our case, we didn't determine eosinophilia in blood periferic smear and high level of Ig E.

In present case; the lack of history, physical and laboratory findings to explain elevation of AST and ALT; decrease of the enzyme levels after completing the series of hepatitis B vaccination, suggested that hepatitis B vaccine could be responsible for this clinical picture.

In conclusion, it is prudent to keep in mind that hepatitis B vaccine can be responsible for the hepatotoxicity.

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