Engerix-B Vaccine Induced Transient Hepatitis B Surface Antigenemia: A Case Report and Review of the Literature

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Abstract

This report describes a case of positive hepatitis B Surface Antigen (HBSAg) following immunization with hepatitis B (HepB) vaccine, which was administered as indicated by negative anti-HBS screen performed prior to initiation of hemodialysis (HD). Variations in HBSAg seropositivity following HepB vaccination reported in the literature has been attributed to the type of HepB vaccine administered, vaccine dose, method of immunoassay used for testing and pharmacokinetics. Clinical implications, complications and the duration of HBSAg seropositivity of this case further affirms current evidence on hepatitis B Surface (HBs) antigenemia following vaccination.

Keywords: Hepatitis B; Hepatitis B surface antigen; Antigenemia; False positive; Engerix-B

Abbreviations

HBSAg: Hepatitis B Surface Antigen; HepB Vaccine: Hepatitis B Vaccine; mg: Milligram; eGFR: Estimated Glomerular Filtration Rate; AF: Atrial fibrillation; HD: Hemodialysis; HBs Antigenemia: Hepatitis B Surface Antigenemia; DNA: Deoxyribonucleic Acid; rt-PCR: Reverse Transcription Polymerase Chain Reaction; HBV: Hepatitis B Virus

Case Description

In February 2017, an elderly female walked into to the outpatient medical clinic with a 6-month history of worsening breathlessness on exertion. She also had worsening paroxysmal nocturnal dyspnea, oliguria, intermittent swelling of bilateral lower limbs and postural dizziness over 3 months. She had a past medical history of hypertension, hyperlipidemia and chronic kidney disease but no history of anemia or per-rectal bleeding/melena. She had recently returned to Singapore after living in Australia for 6 years, during which her medical conditions were managed by a community physician. She was never on follow-up with a specialist cardiologist or nephrologist.

Clinically she was afebrile, normotensive, not uremic, and not jaundiced. Initial investigations revealed normocytic normochromic anemia (Hb 6.5 g/dL) and end-stage renal failure (ESRF) with a creatinine of 768 µmol/L (eGFR <15 mL/min) and urea of 31.1 mmol/L. Ultrasound scan of the kidneys showed bilateral simple renal cysts with background renal parenchymal disease. She was also noted to have atrial fibrillation (AF) on electrocardiogram and transthoracic echocardiogram revealed dilated atria, moderate mixed aortic valve disease and normal left ventricular ejection fraction. Liver function tests (including serum albumin and total protein) and prothrombin time/international normalized ratio were within normal reference range.

She was fluid restricted and started on rate control medications for AF, erythropoetin and intravenous iron replacement therapy (Ferritin 134.5 ng/mL and transferrin saturation 13.07%). Eventually, she was initiated on HD via a PermCath following a routine pre-dialysis screen for hepatitis B, hepatitis C and HIV.

According to the screening tests, the patient was negative for hepatitis B but not immunized against it (Table 1). Thus she was vaccinated with 1 mL (10 mcg) Engerix-B (GlaxoSmithKline, Brentford, London). Two days following vaccination a second HBsAg screening was mistakenly ordered and processed which showed a strongly reactive HBsAg. This abnormality prompted further investigation with other hepatitis B serology tests on pre-vaccination specimens and, a repeat HBsAg and Hepatitis B DNA reverse transcription polymerase chain reaction (rt-PCR) quantitation tests at 5 days post-vaccination. Anti-HBc IgM on pre-vaccination specimen was nonreactive and Hepatitis B DNA rt-PCR on post-vaccination specimen was below detection limits (<13.5 IU/mL) ruling out recent hepatitis B virus (HBV) infection. In addition, post-vaccination (day 5) investigations demonstrated a diminishing HBsAg reactivity. Furthermore, liver
function tests remained within the normal reference range before and after vaccination (Table 1).

Table 1 Progression of results of hepatitis B antigen and antibody testing from the day of vaccination. HBsAg was strongly reactive 2 days following vaccination. Other serologies were tested retrospectively on stored samples (in italics) when the unexpected HBsAg result was found. NR: non-reactive, R: reactive.

<table>
<thead>
<tr>
<th></th>
<th>Day 0 (Prior to Vaccination)</th>
<th>Day 2</th>
<th>Day 5</th>
<th>Day 21</th>
<th>Liver function tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>NR(0.156S/CO)</td>
<td>R(7.640s/CO)</td>
<td>R(3.908S/CO)</td>
<td>NR(0.365S/CO)</td>
<td>Bilirubin(total) 5.7 (&lt;14umol/L)</td>
</tr>
<tr>
<td>Anti-HBs</td>
<td>1 IU/L</td>
<td>0 IU/L</td>
<td>0 IU/L</td>
<td>138 IU/L</td>
<td>Albumin 38 (34-48g/L)</td>
</tr>
<tr>
<td>HBeAg</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>ALT 7 (10-36U/L)</td>
</tr>
<tr>
<td>Anti-HBe-IgM</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>AST 11(10-30U/L)</td>
</tr>
<tr>
<td>Anti-HBe</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>ALP 63(40-150U/L)</td>
</tr>
<tr>
<td>HepB DNA PCR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>GGT 9(9-36U/L)</td>
</tr>
<tr>
<td></td>
<td>NR (&lt;13.5IU/mL)</td>
<td></td>
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</tbody>
</table>

The patient was advised that the abnormal HBsAg result is likely spurious due to premature re-testing following vaccination, as subsequent tests (anti-HBc IgM and hepatitis B DNA rt-PCR) yielded negative results. She was discharged to outpatient HD without segregation into the hepatitis positive cohort and subsequently transitioned to peritoneal dialysis according to her preference. She received follow-up re-testing at 21 days post-vaccination which demonstrated a non-reactive HBsAg and positive immunization status (anti-HBs 138IU/L/L).

Discussion

The HBV is a DNA virus that is unique in its genomic and antigenic structure and replicative cycle [1]. Globally it is estimated that 248 million people are chronically infected with HBV [2]. It can lead to acute or chronic hepatitis, and causes much of the morbidity and mortality from acute and chronic liver disease [3]. Approximately 5% of infected adults develop chronic HBV infection and of whom, 15-40% will develop liver cirrhosis and its complications, including hepatocellular carcinoma [4,5]. Positive HBsAg test indicates presence of the surface antigen in serum, representing either an acute or chronic hepatitis B infection, with chronic infection differentiated by absence of anti-HBc IgM [6]. As our patient’s anti-HBc IgM serology and DNA viral load were negative with a recent history of HepB vaccination (Engerix-B), an alternative diagnosis of false positive HBsAg secondary to vaccination was entertained. The vaccine induced antigenemia resolved at 21 days post-vaccination.

HepB vaccination is the most effective measure to prevent HBV infection and its sinister consequences. It has been the mainstay of comprehensive strategies employed to eliminate HBV, since recommendations for HepB vaccination which were first issued in 1982 [7,8]. The plasma derived HepB vaccine which became available in 1982 was initially recommended for individuals at high risk, whereas Yeast-derived (Saccharomyces cerevisiae) recombinant DNA HepB vaccines became available in 1986 [9]. As targeted vaccination to high-risk groups proved ineffective in decreasing the incidence rates, in 1991, the Committee on Infectious Diseases of the American Academy of Paediatrics and the Advisory Committee on Immunization Practices recommended universal immunization of infants against hepatitis B [10]. World Health Organization (WHO) called for the introduction of HepB vaccine into all national vaccination programs in 1992 [11]. Effective vaccination programs are proven to prevent HBV infection in 95% of immunized individuals [5].

Since late 1980s questions had arisen whether a transient antigenemia could occur in recently vaccinated individuals. Katkov et al. [12], in 1989 concluded that the presence of HBsAg in the blood cannot be attributed to recent vaccination, as neither 1-hour nor 24-hour post-vaccination HBsAg levels were detectable. However, case reports of vaccine induced HBsAg false seropositivity have been documented among adults [13-27] and in children/ neonates since 1993 [9,28-33], particularly in the context of screening for hepatitis among recently vaccinated individuals. Although it is not a frequent clinical presentation, unawareness of this phenomenon could lead to unnecessary investigations, additional healthcare cost [34] and, impact on patient and staff psyche [19,27]. Perhaps it is important to notice that Katkov et al. [12] findings could have been secondary to testing of HBsAg within 24-hours post-vaccination, lower vaccine dose and the type of vaccine used, which is Heptavax (Merck Sharp & Dohme, West Point, PA) [19].

Literature suggests that the changes and variations observed in antigenemia among vaccinated individuals are probably due to the method of immunoassay and the type of HepB vaccine administered [34]. This vaccine-assay cross-reactivity is due to the similarity between the immunologically active epitope of the recombinant vaccine and the target epitope of the immunoassay [35]. In the case of our patient, HBsAg screening was performed by Abbott Architect System (Abbott Laboratories, Lake Bluff, IL, USA) HBsAg Qualitative II test, which is a single step chemiluminescent microparticle immunoassay. All in all, it is important to understand that HBs antigenemia is caused by passive transfer of antigen and not by viral replication [27].
Interestingly, most of the available HepB vaccines have been reported to give rise to a transient antigenemia in healthy individuals as well as in patients with multiple co-morbidities. Engerix-B [13,18,20,27,29,30], Infanrix (GlaxoSmithKline, Brentford, London) [9], Twinrix (GlaxoSmithKline, Brentford, London) [16], Pediarix (GlaxoSmithKline, Brentford, London) [33], Hepavax-Gene (Green Cross Vaccine Corp., Seoul, South Korea) [18,22], and GenHevac B (Pasteur Institute, Paris, France) [22,28] vaccines are known to cause HBs antigenemia. However, despite significant differences in prevalence of post-vaccination antigenemia with certain vaccines, immunogenicity has been reported to be satisfactory and comparable [18].

Janzen et al. [19] observed female predominance among patients with positive HBs antigenemia and vaccine dose per kilogram was also noted to be slightly higher in the group of patients with positive serology. It has been postulated that variable tissue absorption, body composition, and blood flow in muscles could have affected the plasma concentration of vaccine antigen [19,27]. Antigenemia has been reported up to a maximum of 21-days post-vaccination [19,28] and multiple studies have recommended that hepatitis screen for individuals should be deferred up to 28-days post-vaccination [26]. A clinical trial that studied the kinetics of vaccination induced HBs antigenemia in healthy young medical student volunteers reported antigenemia up to 5 days post-vaccination [18]. Therefore, it has been recommended that potential blood donors who recently received HepB vaccine should be temporarily deferred [19,25,26].

This phenomenon has been observed in various populations and subgroups of patients including neonates, young healthy blood donors [16] and elderly ESRF patients on HD [17]. Vaccine induced false positive HBsAg spans all ages and patients are generally asymptomatic. However, persistent unconjugated hyperbilirubinemia and transaminasemia mistakenly diagnosed as acute hepatitis in a 70 day-old breastfeeding boy had been reported [9].

Vaccine interference with immunological screening assays extends beyond hepatitis B. Seasonal influenza vaccines have been implicated in false positive HIV serology tests [36]. Conversely, false negative HBsAg serology as a result of mutations in the HBsAg epitope “a” allow immunological escape [37], highlighting the importance of clinical correlation when evaluating serological abnormalities especially in the context of unexpected screening results. Furthermore, false negative HBsAg has been reported among patients with chronic liver disease [38], and among healthy HBV DNA carriers [39], making it impossible to exclude all infectious blood donors by serologic screening tests for hepatitis B [40].

Accurate clinical assessment including vaccination history would help minimize the risks and implications of false positive HBsAg results. If confirmatory testing is clinically indicated, additional investigations with anti-HBc IgM, and hepatitis B DNA rt-PCR (viral load quantification) would be useful in practice. Based on our experience and review of the existing literature, screening for hepatitis B should be best avoided until after 4 weeks (28 days) [17,20] from HepB vaccination in order to prevent misdiagnosis, and anxiety caused to the patient and staff.

**Points to remember**

Hepatitis B vaccination can induce transient HBsAg reactivity, in all ages and various levels of renal function (from normal to ESRF). This cross-reactivity is due to the recombinant vaccine epitope being derived from the same target epitope used in various immunoassays (Hepatitis B surface antigen epitope “a”)

Accurate clinical history regarding recent vaccinations would help minimize the risk of false positive HBsAg due to pre-mature screening for hepatitis.

Vaccination may induce antigenemia in a significant proportion of patients (up to 50% in one study), which may persist from 2 days up to 28 days and it will depend on the type of vaccine, dose and HBsAg immunoassay.

If urgent confirmatory testing is clinically indicated, additional investigations with anti-HBc IgM, and Hepatitis B DNA rt-PCR will help clarify the cause for HBs antigenemia.

Blood donors and HD patients are at higher risk for vaccine induced false positive HBsAg results when they are subject to regular hepatitis B screening.

Published evidence suggests delaying hepatitis B screening at least for 21-28 days following hepatitis B vaccination.

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**Conflict of interest**

Authors declare no conflict of interest.

**References**


