CASE REPORT

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Post-booster response after undetected anti-HBS antibody level in an 8-year-old girl with an up-to-date Hepatitis B immunization: a case report

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ABSTRACT

Introduction: Hepatitis B immunization is stated in Indonesia's child immunization policy. It consists of four doses of a combination vaccine containing HBV, following a monovalent birth dose, to provide immunity against the Hepatitis B virus (HBV) infection in childhood. Anti-hepatitis B surface antigen (HBsAg) antibodies (anti-HBs antibodies) as low as 10 IU/L are considered protective. Undetected anti-HBs antibodies after an up-to-date immunization still occur and are worrisome for parents. Booster immunization is an option to achieve a good anamnestic response. Pre-booster anti-HBs antibodies below 2 IU/L predict a poor post-booster response.

Case Report: An 8-year-old girl with an up-to-date HBV was taken to the outpatient clinic to assess the need for a booster Hepatitis B immunization. Her parents felt that their daughter frequently had common colds since elementary school, so a general check-up was done abroad. Undetected anti-HBs antibody levels after an up-to-date HBV immunization were found, so her parents wanted to know the meaning of the undetected anti-HBs antibody level and why it happened. She had no complaints at the time of the examination, and there was nothing remarkable from the physical examination. This patient was deemed unprotected against subsequent HBV infection and received a Hepatitis B booster immunization. Despite the undetected anti-HBs antibodies, a good anamnestic response was achieved.

Result: A good anamnestic response following a booster immunization was proven by a laboratory examination one month later.

Conclusion: Anti-HBs antibody levels < 10 IU/L warrant a booster immunization, regardless of the pre-booster level. It is beneficial to measure the post-booster level to determine the next action. Further research should be done to further explore this topic.

Keywords: booster HBV immunization, protective anti-HBs antibody, up-to-date immunization.
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INTRODUCTION

Many countries launched an immunization schedule that involves administering the Hepatitis B vaccine 3–4 times within the first year of life.[1–3] In Indonesia, the Hepatitis B vaccine is given within the first 24 hours of birth, followed by four doses of the Hepatitis B immunization.[4] The agreed protective level of anti-HBs antibodies is 10 IU/L.[5] Countries report different ages at which seroprotective levels above 10 IU/L can still be maintained.[3,6-8]

Protective serum anti-HBs antibody levels are usually maintained between 16 and 30 years.[3,6-8] Although decreasing seroprotective hepatitis B levels over time is common, undetected anti-HBs antibody levels are a serious concern for parents.[3] Booster immunizations following pre-booster serum anti-HBs antibody levels below 3.3 IU/L did not yield satisfactory results.[6]

A booster dose, following a low antibody l evel, can improve the protective level against future infection.[3] Females show a better response to booster immunization compared to males.[3] An anti-HBs antibodies below 2 IU/L predict a poor post-booster response.[3] This case proves that, regardless of the pre-booster level, a booster immunization should be provided. A measurement of anti-HBs antibodies four weeks after the booster should be done to help with the next step.

CASE PRESENTATION

We present the case of an 8-year-old healthy Asian girl with undetected anti-HBs antibody levels after an up-to-date HBV immunization using vaccine products from three different manufacturers. This child was taken to the outpatient clinic to assess the need for a booster Hepatitis B immunization. Her parents felt that their daughter frequently had common colds since elementary school. Being a

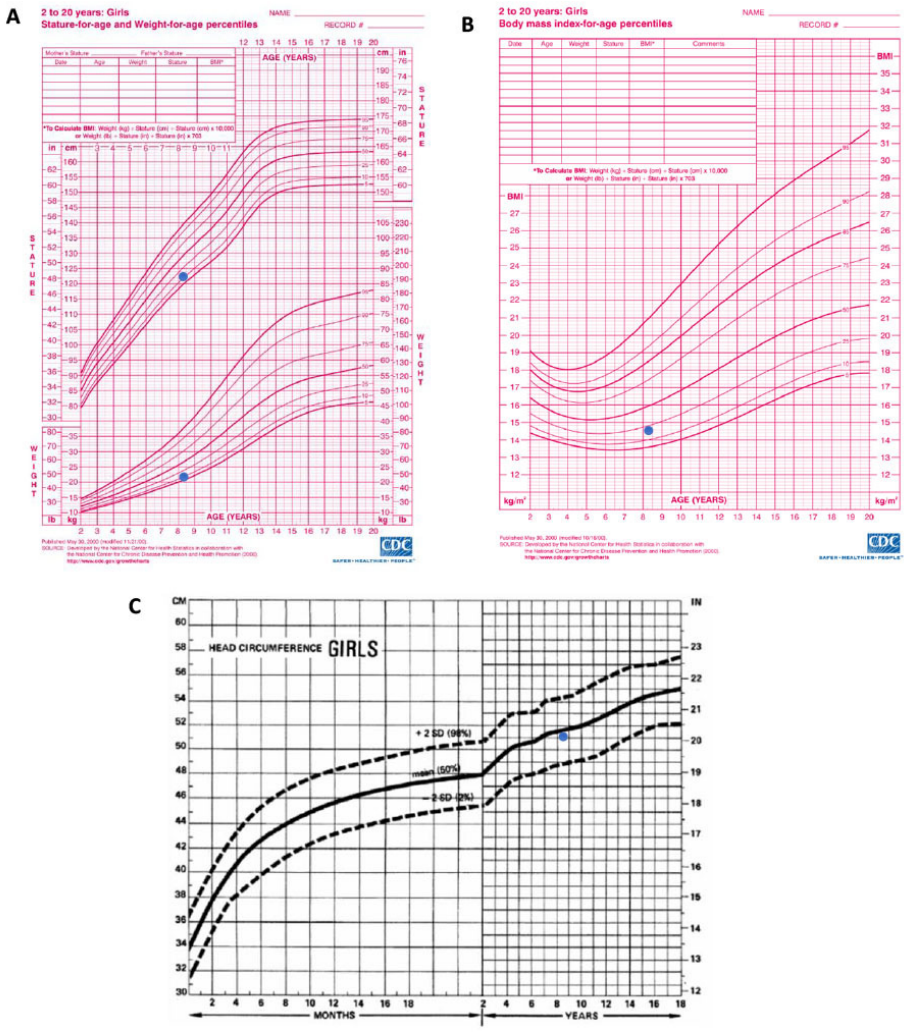

Figure 1. Growth parameter of the patients. A. Stature-for-age and height-for-age percentiles: CDC, B. Body mass index-for-age percentiles: CDC, C. Head circumference girls: Nellhaus.

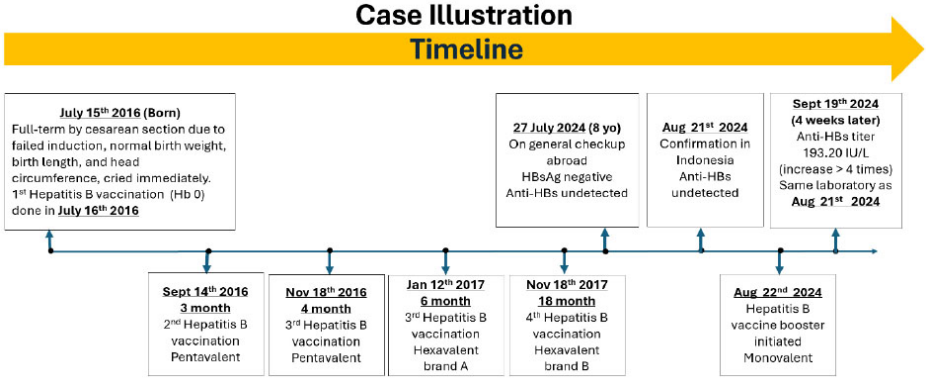

Figure 2. Timeline of the case report.

middle-income family, they decided to do a general check-up abroad, with the anti-HBs antibody level examination included as part of the check-up. Her parents also want to know the meaning of the undetected anti-HBs antibody level and why it happened.

She had no complaints at the time of the examination (August 22nd, 2024). No cough, runny nose, or fever was found. She has a good appetite with no problem with urination and defecation. She has a dust and mite allergy and has no exposure to cigarettes or pets. Her growth and development are typical of her age. The growth parameters were as follows: body weight 22 kg (CDC, P_{10-25}), body height 123 cm (CDC, P_{10-25}), body mass index 14.5 (CDC, P_{10-25}), and head circumference 51cm (Nellhaus, -2 to 0 SD) (Figure 1). This patient was alert with an appropriate response to the question asked of her. There is nothing remarkable from the physical examination. Despite the frequent upper respiratory tract infection, there was no significant problem with her general condition. This patient, her brother, and her parents had no genetic abnormalities or chronic diseases. This patient has never been hospitalized before.

She was born full-term by cesarean section due to failed induction, with normal birth weight, birth length, and head circumference. She cried immediately after birth and had mild jaundice at three days of age. Her blood type is O Rh+. She is the firstborn of two children. She was breastfed until she was nine months old.

A complete blood test, thyroid-stimulating hormone (TSH), blood glucose, and urinalysis examination on July 27th, 2024, were within normal limits. Carcinoembryonic antigen (CEA) was 0.9 µg/L (<5.1 µg/L). Rapid Plasma Reagin (RPR) was non-reactive. Human Immunodeficiency Virus (HIV)-1 and 2 Ag/Ab were not detected. Quantiferon TB was negative. Neither HBs Ag nor anti-HBs antibodies were detected (assessed using Electrochemiluminescence Immunoassay). The total Hepatitis A antibody (anti-HAV, assessed using Electrochemiluminescence Immunoassay) was detected. A chest X-ray revealed no significant abnormalities in the lungs or heart. A Water's view X-ray found maxillary sinusitis, with adenoid and palatine tonsil enlargement. The parents willingly pay for a second anti-HBs antibody measurement in Indonesia, since the comparison of pre-booster and post-booster immunization should be done using the measurements.

The booster immunization successfully increased the anti-HBs antibody level by more than four times (193.20 IU/L) four weeks later, indicating a good anamnestic response. The timeline can be seen below (Figure 2).

DISCUSSION

Chronic Hepatitis B infection can lead to the occurrence of cirrhosis and cancer, which can result in a premature death.[4] Two hundred fifty-four million people worldwide are estimated to suffer from Hepatitis B, with 12 % of them being children.[5] An estimated 1.3 billion people died due to hepatitis infection, similar to the deaths caused by tuberculosis infection in 2022.[5] Being one of the most effective and successful vaccines, known for more than four decades, the Hepatitis B vaccine can prevent it.[6] Immunization is one of the most cost-effective medical interventions, estimated to save about 2.5 million lives yearly by protecting against infectious agents, such as viruses, bacteria, or parasites, through a complex interaction between innate, humoral, and cell-mediated immunity.[9] Four doses of a combination vaccine containing HBV, following a monovalent birth dose, are deemed needed to provide immunity against the HBV infection in childhood by Indonesia's child immunization policy.[7] About 45% newborns worldwide received the first Hepatitis B vaccine within the first day of their lives.[5] There is a significant decline in chronic Hepatitis B infection found in under-5-year-old children globally after hepatitis B vaccine implementation in the national childhood immunization programs.[8] This patient received an up-to-date immunization.

Generally, 90% of the population will have protective anti-HBsAg antibodies after three doses of the Hepatitis B immunization.[9,10] Various studies have shown that between 5% and 15% were low or non-responder, meaning that antibodies formed were either below the protective threshold or not formed at all.[6] In 2016, the WHO launched the Global Viral Hepatitis Strategy, which aims to eliminate HBV by 2030 by increasing the number of individuals with protective anti-HBs antibodies.[4] Anti-HBsAg antibodies after immunization indicate an anti-viral response from CD4+ T cells that function well and produce anti-HBV neutralizing antibodies.[11] Arbitrarily, anti-HBsAg antibodies are defined as those above 10 IU/L.[12] Several factors influence vaccine responses, including intrinsic, perinatal, and extrinsic host factors, as well as behavioral, nutritional, environmental, vaccine, and administration factors.[9,13] Several factors known to affect immunity to HBV in fully vaccinated individuals include obesity, cigarette exposure, old age, gender, genetic factors, and concomitant diseases such as renal failure, HIV infection, HCV infection, diabetes mellitus, and cancer.[10,11] The population's compliance with immunization, proper handling of vaccines, immunocompetency of the host, as well as immunosuppressant drugs, are significant determinants in vaccine effectiveness. This patient is a healthy girl with no clear intrinsic, perinatal, or extrinsic host risk factors. She also has no behavioral, nutritional, or environmental factors. There also appeared to be no issues with vaccine administration, although the vaccines she received came from different brands and manufacturers. Both were second-generation recombinant Hepatitis B vaccines from trusted brands that should offer comparable immunogenicity. This patient's initial immune response after completing the schedule was not assessed, so there was no data regarding its protective level.

An anti-HBsAg antibody level measurement can be done using various techniques, such as Enzyme-Linked Immunosorbent Assay (ELISA), Radioimmunoassay (RIA), Chemiluminescence Immunoassay (CLIA/CMIA/ECLIA), Fluorescent Immunoassay (FIA), Lateral Flow Immunochromatographic Assay (rapid test), Neutralization/Functional Assay, Western Blot/Immunoblot, and Multiplex Bead-based Assay. Every method has its advantages and disadvantages.[14–16] They have different sensitivity and specificity.[17] This patient was assessed using the Electrochemiluminescence Immunoassay (ECLIA) method. This method has high sensitivity, is automated, and offers high throughput and quantification.[17] The downfall of this method is the requirement for expensive equipment and trained personnel. It can detect down to 2-5mIU/ml of anti-HBs, with a sensitivity of 99%, a specificity reported as 99%, and an intra-assay coefficient of variation of less than 10%.[17] The low intra-assay coefficient makes this method suitable for repeated clinical monitoring. Despite its advantages and disadvantages, ECLIA is commonly used in modern hospital labs due to its automation. It replaces ELISA, a gold standard in many labs. The undetected anti-HBs antibody levels were measured using ECLIA, which has an excellent sensitivity and specificity. The undetected anti-HBs antibody levels mean it was truly far below the protective level.

An anti-HBsAg antibody level between 10 and 100 IU/L is considered weakly protective, and levels above 100 IU/L are considered strongly protective.[18] Protective antibody levels tend to decrease over time, especially during the first years after immunization.[10] In some individuals, protective antibodies can decrease to a level that is undetectable in the blood.[11] Di Lello et al., reported anti-HBs levels lower than 10 mIU/mL in approximately 20% of the 5-year post-immunization cohort.[10,12] Rampengan et al., also reported that only 23 of 105 (21.9%) children aged 10-15 years had detectable anti-HBs, with only two having levels ≥100 mIU/mL.[19] Generally, an anti-HBsAg antibody level ≥ 10 IU/L is considered protective.[6] A patient with an anti-HBsAg antibody level below 10 IU/L needs a booster.[6,20] This patient has undetected anti-HBsAg antibody levels at the age of 8 years. It implies that there was no protection against subsequent HBV infection, despite up-to-date immunization. This patient needs a booster.

The Centers for Disease Control (CDC) recommends that children without a protective level of antibodies (anti-HBs) after receiving basic immunization before 1 year of age, should receive one booster immunization.[21] If it fails to generate a protective level, a three-injection series is used as the second series. A failure to obtain a protective level after 6 doses of vaccination does not need another immunization.[22] Thirty to fifty percent of them will achieve a protective level.[1,14] A pre-booster anti-HBs level >2 mIU/mL is predictive of a prompt response to a booster immunization.[3] Females show a better response to booster immunization compared to males.[3] Despite the pre-booster anti-HBs level being < 2 mIU/mL, this patient showed a good response after only one dose of the booster vaccine. The patient's unprotected condition was found

during a general check-up, since there was no proof regarding her pre-booster anti-HBs level earlier, a booster is needed. This patient received one dose of the booster immunization, and surprisingly, her anti-HBs level increased markedly to above 100 IU/L. As a result, the second series was not administered. Immunocompetent host with good anamnestic response following a challenge dose are deemed protected, regardless of subsequent decline later.

Based on long-term follow-up studies, Hepatitis B immunization in infancy/adolescence confers immunity that lasts for more than 15 years, even when anti-HBs levels decline.[19,23–25] A small but persistent pool of long-lived plasma cells and memory B cells remains in the body, capable of being reactivated by re-exposure to HBsAg. Upon booster administration, these cells rapidly differentiate into antibody-secreting plasma cells. The T follicular helper cells are involved in this process, causing the antibody titters to rise swiftly and an improvement in affinity. This mechanism explains how a booster can effectively modulate the immune system to re-induce protective antibodies in individuals whose baseline levels have waned.[26,27] The significant increase in anti-HBs level proves a good immunity response following a booster immunization.

Rusmil et al., reported that 11 of 144 (7.6%) infants had anti-HBs levels <10 mIU/mL, classified as poor responders, after basic Hepatitis B immunization. Six months later, eight children (72.2%) still had levels <10 mIU/mL and were given the second series of Hepatitis B immunization, which resulted in all subjects achieving protective levels (>10 mIU/mL).[20] Another study by Anderson et al., in 106 German teenagers, revealed that 40% of subjects had anti-HBs levels <10 mIU/mL, and after receiving a booster vaccine, almost all (97%) teenagers achieved anti-HBs levels ≥100 mIU/mL, regardless of their pre-booster levels.[13] The CDC reported that 15% to 25% of non-responders from the first series of Hepatitis B immunization will respond after one additional dose, and 30% to 50% will respond well after three additional doses.[1,14] This fact implies the importance of memory immunity, as even in the absence of anti-HBs, a significant amount of HBsAg-specific memory T and B cells are still detected in vaccine responders.[28] Hepatitis B booster vaccine doses are not needed in immunocompetent hosts, despite the decline in anti-HBs levels over time. However, it must be noted that the declining anti-HBs levels could potentially cause a problem for high-risk groups.[10,13] Should her anti-HBs antibody level decrease or become undetected later, there is no need to administer another booster immunization, as there is evidence that she is responsive to the vaccine, unless there is a high-risk environment for Hepatitis B virus infection at that time. To eliminate viral hepatitis by 2030, a significant boost in testing and treatment, preceded by effective immunization, must be achieved. It is crucial to ensure that, despite our efforts to vaccinate children, a protective anti-HBsAg antibody level is achieved. There was a good anamnestic response, although the pre-booster anti-HBs level was below 2 mIU/mL, which predicts a poor response to a booster immunization. No further booster is needed, even if low anti-HBs levels were found.

Although very effective and safe, some adverse events still occur.[8] Gong et al., reported adverse events following immunization reporting rates (i.e., vaccine-product-related reactions, immunization anxiety-related reactions, and coincidental events) from 2011 to 2023 as 17.55/100,000 doses, with 98.73% of them being non-serious.[8] Most vaccine product-related reactions, such as local reactions at the injection site, fever, and rash, occur within the first 3 days after immunization.[8] Coincidental events, such as death, can also be found after immunization.[8,29] This patient showed no adverse events nor coincidental events.

The strength of this case report lies in the fact that the patient is a long-time patient of the treating physician, with a known health history dating back to infancy. Being a long-time patient, any adverse events following immunization will surely be known and reported. The booster vaccination achieved a protective level. A limitation of the case report is the absence of prior laboratory evidence regarding the patient's immune competence. The effectiveness of this vaccine depends on many factors, among others, the host's immune competency.

CONCLUSION

A booster immunization following an up-to-date HBV immunization might still induce a good anamnestic response in a healthy 8-year-old girl, despite the poor previous anti-HBs antibody level, as evidenced by a strongly protective anti-HBsAg antibody level four weeks later. The need for post-immunization anti-HBs antibody level testing should be further explored in future research.

CONFLICT OF INTEREST

There are no conflicts of interest regarding this study.

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ETHICAL APPROVAL

Informed consent was obtained from her parent before publication since she is still a minor, and this article does not require ethical approval.

AUTHORS' CONTRIBUTIONS

Lisa is the treating physician. Lisa performed the data collection. Lisa and Budiyanto drafted the manuscript. Lisa and Budiyanto provided critical revisions.

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