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Journal of Pediatric Nephrology

Original Article

Anti-HBs Titer in Children With Nephrotic Syndrome Admitted to a Tertiary Care Hospital

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Citation Akter A, Hossain D, Khanam W, Adnan MA, Zaman Kh, Sultana A. Anti-HBs Titer in Children With Nephrotic Syndrome Admitted to a Tertiary Care Hospital. Journal of Pediatric Nephrology. 2023; 11(2):58-64. https://doi.org/10.22037/jpn.v12i2.42987

https://doi.org/10.22037/jpn.v12i2.42987

Article info:
Received: 4 Aug 2022
Accepted: 12 Jan 2023
Publish: 01 Apr 2023

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ABSTRACT

Background and Aim: Nephrotic syndrome (NS) is the most common pediatric renal disease. Immune dysregulation, prolonged immunosuppressive treatment, and recurrent prolonged proteinuria in NS cause alterations in serum immunoglobulins, especially hypogammaglobulinemia. Thus, anti-HBs titer may be reduced in NS patients. We assessed anti-HBs titer among hepatitis B-vaccinated children with NS.

Methods: This case-control study was conducted at the Department of Paediatrics of the Institute of Child & Mother Health, Dhaka, from July 2020 to June 2021. Sixty-one children with primary and recurrent NS previously vaccinated according to the expanded programme on immunization program were evaluated for anti-HBs titer and compared with 61 age- and sex-matched healthy children.

Results: Protective anti-HBs titer was found in 29(47.5%) and 40(65.6%) cases in the case and control groups, respectively. The mean anti-HBs titer was 37.2±35.5 IU/L in the case group and 55.7±28.3 IU/L in the control group, which showed a significant difference between the groups. The mean anti-HBs titer was 52.9±35.5 IU/L in the first attack, 33.9±36.8 IU/L in the infrequent relapse nephrotic syndrome (IFRNS), and 22.2±27.41 IU/L in the frequent relapse nephrotic syndrome (FRNS), respectively. The difference was also significant statistically. The mean anti-HBs titer was lower in the FRNS and IFRNS and significant in the FRNS compared to the first attack. The mean anti-HBs titer was significantly ($P<0.05$) lower in the IFRNS and FRNS compared to the controls.

Conclusion: Anti-HBs titer was found significantly lower than the protective level in the first attack and relapse cases of NS.

Keywords: Nephrotic syndrome, Anti-HBs titer, Hepatitis, Immunity

Introduction

Nephrotic syndrome (NS) is the most common renal disease in children with an annual incidence of 2-7 per 100000 and a prevalence of 12-16 per 100000 children [1]. The incidence is higher in South Asia, 9-10 per 100000 children [2]. NS is characterized by heavy proteinuria (>3.5 g/24 hr or urine protein: Creatinine ratio >2), hypoalbuminemia (≤2.5 g/dL), generalized edema, and hypercholesterolemia (>200 mg/dL) [3]. About 80-85% of NS cases are steroid sensitive (SSNS), which

include frequent as well as infrequent relapsing NS and steroid-dependent NS, and the remaining 15-20% are steroid-resistant (SRNS) [4].

The main pathogenesis in NS is increased glomerular permeability. The glomerular basement membrane (GBM) acts as a selective barrier in the nephron. Normally, larger proteins are not filtered through the barrier due to their negative charge. T cell dysfunction as well as humoral immunity is altered in NS [5]. An abnormal immunogenic response to some unknown stimuli causes the suppression of T cell function. It causes the release of various interleukins, cytokines, and mediators, which act on GBM and change its negative charge into positive. Positively charged GBM filters negatively charged albumin and results in proteinuria. Also, damage to the GBM component by an unknown mechanism increases the leakage of albumin, high molecular weight proteins, such as IgG, anti-HBs antibody, etc. [6]. Loss of urine, impaired reabsorption by tubular cells, and decreased production cause a decrease in level of immunoglobulins, especially IgG. Thus, hypogammaglobulinemia is a frequent finding in NS. On the other hand, the prevalence of hepatitis B surface antigenemia is significantly higher in nephrotic patients compared to the general population [7].

Hypogammaglobulinemia increases the chance of infection. These children are at an increased risk of acquiring various infections, including hepatitis B virus (HBV) infection due to repeated hospital admission and prolonged immunosuppressive therapy [2]. HBV infections in childhood have a higher chance of chronicity and can lead to chronic hepatitis, cirrhosis, and hepatocellular carcinoma [2].

Many preventive measures have been employed to prevent HBV infection, including screening of blood donors, preparation of plasma-derived products in a way that inactivates HBV, implementation of infection control measures, administration of hepatitis B immunoglobulin, and vaccination [8]. Hepatitis B vaccine has been included in the expanded program on immunization (EPI) since 2004 in Bangladesh and since 2009 as part of the pentavalent vaccine at 6, 10, and 14 weeks [9]. Anti-HBs titer ≥10 IU/L is considered protective immunity [10].

Nephrotic children have lower seroconversion to the vaccine because of immune dysregulation, prolonged immunosuppressive therapy, and recurrent prolonged albuminuria [11]. This study was done to determine anti-HBs titer among HBV-vaccinated NS children.

Materials and Methods

This case-control study was carried out at the Department of Pediatrics, Institute of Child and Mother Health (ICMH), and Department of Virology, BSMMU-Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka from July 2020 to June 2021.

All vaccinated children aged 2-12 years with first attack and relapsing cases of NS admitted to the Department of Pediatrics, ICMH, during the study period were considered cases. Age- and sex-matched healthy vaccinated children attending the outpatient department of pediatrics, ICMH, during the study period were enrolled as controls.

Children receiving an intravenous blood product/immunoglobulin within three months and those with a secondary cause of NS, SRNS, positive or active HBV infection, and unimmunized or incompletely vaccinated subjects according to the EPI schedule were excluded.

The following standard formula (Equation 1) was used to determine sample size:

$$1.\ n = \left[\frac{Z\alpha\sqrt{2p(1-p)} + Z\beta\sqrt{p_1(1-p_1)+p_2(1-p_2)}}{P_1 - P_2}\right]^2$$

n=sample size

P_1=Seroprotection in the case group=37.0% [12]

P_2=Seroprotection in the control group=61.0% [12]

P=(P1+P2)/2

Z_α=1.96 at a 5% level of significance

Z_β=Z value (one-tailed) on standard normal distribution at a definite power that is 1.28 at 90% power.

After calculation, n was found to be 89 but due to time limitations and the COVID-19 pandemic situation, 61 samples were considered in each group (Figure 1).

After selection, case and control data were collected in a semi-structured pre-tested questionnaire. NS patients were divided into three groups depending on the number of attacks and steroid response. Group 1 comprised 22 patients who presented with initial episodes, group 2 comprised 20 patients who had infrequent relapse nephrotic syndrome (IFRNS), and group 3 comprised 19 patients who had frequent relapse nephrotic syndrome (FRNS).

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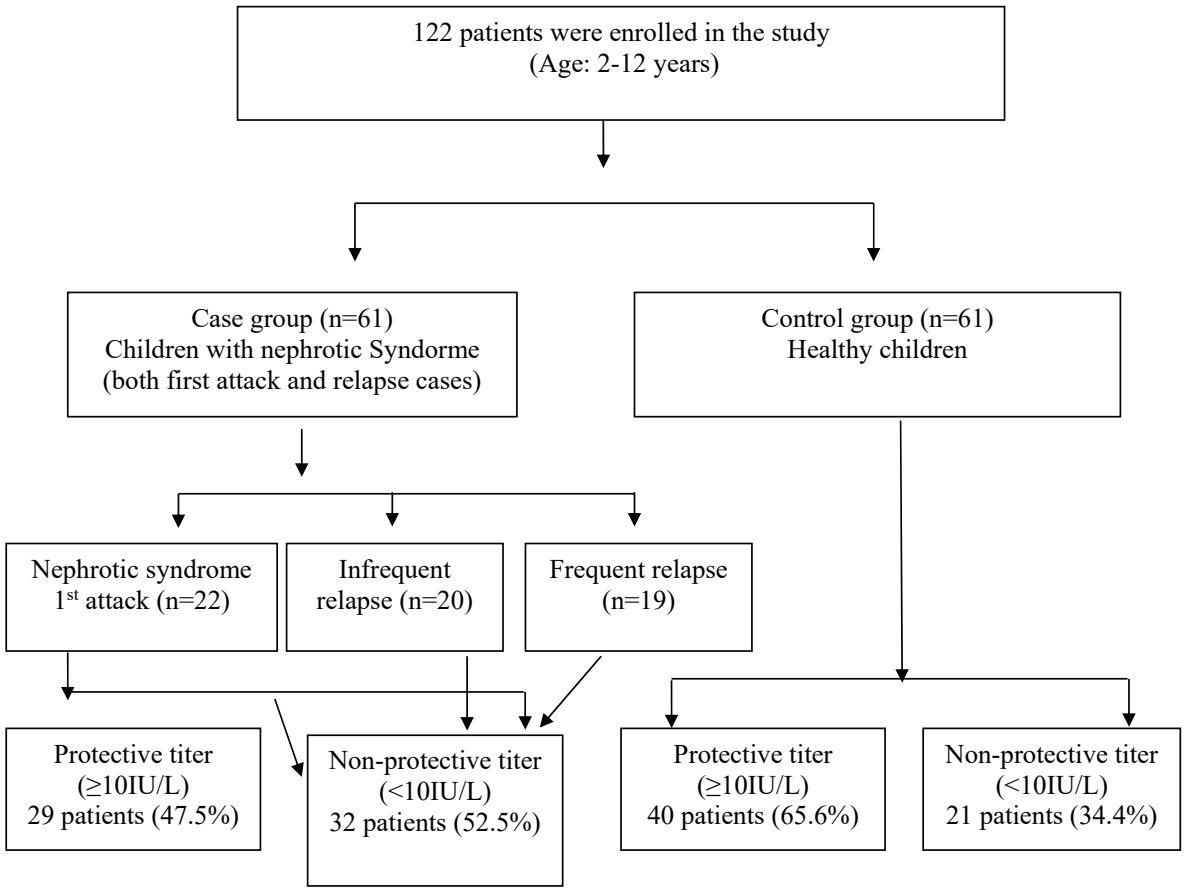

Figure 1. An algorithm showing the anti-HBs titer of the study subject at a glance

Serum albumin, S-creatinine, S-cholesterol, and spot morning urine protein: Creatinine ratio were sent to the Department of Laboratory Medicine, ICMH, Dhaka for both case and control groups. Then, the cases and controls were sent to the Department of Virology, BSMMU, Dhaka for the measurement of anti-HBs titer using the chemiluminescence immunoassay technique where the LIAISON® (Diasorin Ltd) was applied.

NS patients were treated with antibiotics, if required, on the basis of blood and/or urine culture and sensitivity report (namely injectable cephalosporines, amikacin, meropenem, and ciprofloxacin on individual requirement) along with other supportive measurements, if required, i.e. those having gut ischemia needed normal saline administration, fever was managed with paracetamol, anasarca was managed with human albumin administration, etc. Then, all the patients were treated with prednisolone according to the standard protocol. The patients were discharged with prednisolone treatment.

Data were checked and cleaned before being incorporated into statistical software (SPSS software, version 23) and analyzed.

An ethical clearance certificate was obtained from the Institutional Review Board (IRB) of ICMH. Informed written consent was obtained from each legal guardian participating in the study.

Results

A total of 122 subjects (61 cases and 61 controls; 1:1 ratio) were included in this study.

The majority of patients (70.5% in the case and 73.8% in the control group) belonged to the age group of 2-5 years. The mean age was found to be 4.58±2.15 years in the case group and 4.84±2.26 years in the control group. In the case group, there were 33 males (54.1%) and 28 females (45.9%), while in the control group, the numbers of males and females were 34(55.7%) and 27(44.3%), respectively (Table 1).

Table 1. Baseline characteristics of the study subjects (n=122)

Baseline Characteristics		No. (%)/Mean±SD		P
		Case (n=61)	Control (n=61)	
Age (y)	2-5	43(70.5)	45(73.8)	0.509
	6-10	17(27.9)	16(26.2)	
	11-12	1(1.6)	0(0.0)	
		4.58±2.15	4.84±2.26	
Gender	Male	33(54.1)	34(55.7)	0.855
	Female	28(45.9)	27(44.3)	

P were obtained from the unpaired t-test and chi-square test.

Table 2. Anti-HBs titre in different types of nephrotic syndrome (n=61)

Anti-HBs Titer	No. (%)			P (Chi-square Test)
	Type of Nephrotic Syndrome			
	1st Attack (n=22)	IFRNS (n=20)	FRNS (n=19)	
Protective (≥10 IU/L)	14(63.6)	9(45.0)	6(31.6)	0.117
Non-protective (<10 IU/L)	8(36.4)	11(55.0)	13(68.4)	

Table 3. Mean anti-HBs titer in different types of nephrotic syndrome (n=61)

Anti-HBs Titer	Mean±SD			P (ANOVA)
	Type of Nephrotic Syndrome			
	1st Attack (n=22)	IFRNS (n=20)	FRNS (n=19)	
Anti-HBs titer (IU/L)	52.9±35.5	33.9±36.8	22.2±27.41	0.017

Out of 61 cases, 22 patients (36.1%) had the first attack of NS, 20 patients (32.8%) had IFRNS, and 19 patients (31.1%) had FRNS. In the case group, the mean serum albumin levels were 1.90±0.61 gm/dL, mean serum creatinine levels were 0.60±0.15 mg/dL, mean serum cholesterol levels were 388.5±132.6 mg/dL, and mean spot morning urine protein: Creatinine ratio was 5.20±4.5.

Among 61 cases, 29 cases (47.5%) had anti-HBs titer at a protective level (≥10 IU/L), while 32 cases (52.5%) had no protective level of anti-HBs titer and this difference was not statistically significant (Table 2). The majority of patients (63.6%) in the first attack group had protective anti-HBs titer compared to the IFRNS (45.0%) and FRNS (31.6%) groups. In the control group, 65.6% had protective titer, which was almost similar to the first attack group.

The mean anti-HBs titer was found to be 52.9±35.5 IU/L in the first attack group, 33.9±36.8 IU/L in the IFRNS group, and 22.2±27.41 IU/L in the FRNS group, respectively (Table 3) and this difference was statistically significant (P≤0.05).

The mean anti-HBs titer was 45.67±38.41 in 1-2 attacks, 25.34±24.78 in 3-4 attacks, and 18.21±22.22 IU/L in ≥5 attacks (Table 4) and this difference was statistically significant (P≤0.05).

Protective anti-HBs titer (≥10 IU/L) was found in 40 controls (65.6%) and 29 cases (47.5%), while non-protective anti-HBs titer was found in 32 cases (52.5%) and

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Table 4. Effect of the number of attacks on anti-HBs titer (n=61)

Number of Attacks	Mean±SD			P (ANOVA)
	1-2 (n=40)	3-4 (n=8)	≥5 (n=13)	
Anti HBs titre (IU/L)	45.67±38.41	25.34±24.78	18.21±22.22	0.030

Table 5. Anti HBs titer in the study subjects (n=122)

Anti-HBs Titer	No. (%)		P (Chi-square Test)
	Case (n=61)	Control (n=61)	
Protective (≥10 IU/L)	29(47.5)	40(65.6)	0.044
Non-protective (<10 IU/L)	32(52.5)	21(34.4)	

21 controls (34.4%) (Table 5) and this difference was statistically significant.

Protective anti-HBs titer (≥10 IU/L) was found in 29 cases (47.5%) in the case group and in 40 cases (65.6%) in the control group and non-protective anti-HBs titer (<10 IU/L) was found in 32 cases (52.5%) in the case group and 21 cases (34.4) in the control group and this difference were statistically significant.

The mean anti-HBs titer was 37.2±35.5 IU/L in the case group and 55.7±28.3 IU/L in the control group, which was significantly (P≤0.05) higher in the control group than in the case group.

Discussion

This study was conducted to assess anti-HBs titer in children with NS who had been previously vaccinated against HBV based on the EPI schedule.

Age and gender distribution in the current study were comparable to several previous studies. Neupane et al. (2019) analyzed the serological profile of HBV infection as well as anti-HBs titer in 200 children, where there were 100 NS cases and 100 controls, respectively. The subjects were 1-18 years with a median age of 7.4 years in the case group and 7.6 years in the control group [12]. They reported that the difference between the two groups was not statistically significant. In the study by Mantan et al. (2013), the Mean±SD age at presentation was 6.9±3 years [2]. In our study, the majority of cases presented at their first attack of NS while in studies conducted by Neupane et al. (2019) and Mantan et al. (2013), there was a higher proportion of participants who referred in their subsequent NS attacks, respectively [2, 12]. For this reason, the results of the current study were not consistent with these studies.

Neupane et al. (2019) also reported that 60.0% and 55.0% of cases and controls were male, respectively, without any statistically significant difference in gender [12]. The patient cohort of the study by Mantan et al. (2013) was 75 children, of whom 51 cases were male and 24 cases were female [2]. These findings are similar to ours regarding the male predominance.

Neupane et al. (2019) assessed 100 cases, of whom 20 cases (20%) had IFRNS, 32 cases (32%) had FRNS, two cases (2%) had first attack, 16 cases (16%) had SDNS, and 30 cases (30%) had SRNS [12]. Mantan et al. (2013) reported that 42 cases (56 %) had SRNS and 33 cases (44 %) had SSNS [2]. These findings are comparable to our study.

Neupane et al. (2019) reported that the mean serum albumin levels were 3 g/dL, mean serum creatinine levels were 0.65 mg/dL, mean serum cholesterol levels were 187 mg/dL, and the spot morning urine protein: Creatinine ratio was 0.13 (0.06, 0.17) in cases with SSNS and 0.16 (0.12, 0.37) in cases with SRNS [12]. All patients in the current study were in the nephrotic phase, but in other studies, the majority of patients were in the remission phase. Thus, the results are not consistent.

Neupane et al. (2019) reported that 37 cases (37%) had seroprotected titer in the case group and 61 cases (61%) had non-seroprotected titer, which was statistically significant (P≤0.05) [12]. Mantan et al. (2013) in their study showed that 48% of patients had protective titer and 52%

had non-protective titer [2]. These findings suggest that the majority of NS patients had non-protective titers.

In the present study, the mean antibody titer was lower in NS patients than in the controls. Neupane et al. (2019) reported that the median anti-HBs titer was lower in the case group, which is consistent with the current study [12].

In this study, the majority of patients with first attack had protective anti-HBs titer compared to those with IFRNS and FRNS. In the control group, 65.6% had protective titer, which was almost similar to the first attack. This reveals that repeated proteinuria might be responsible for reduced antibody titer in relapse cases.

Neupane et al. (2019) measured the median (IQR) anti-HBs titer in their study subjects, which was 75 mIU/mL in the case group [12]. The frequency of children who were seroprotected was similar among different NS categories as well as among those receiving various immunosuppressants. Most patients were in the remission phase during the study period, which might be the cause of the difference in findings between this and our study. Some research on protection against HBV in children with NS used vaccines with dual shots [2].

The mean anti-HBs titer was significantly lower ($P \leq 0.05$) in the FRNS group compared to the first attack group, which might be due to repeated proteinuria. Frequent proteinuria due to long-term use of immunosuppressive drugs may be the cause of these findings.

Neupane et al. (2019) reported that their 37 subjects (37%) had seroprotected titer in the case group and 61 cases (61%) had non-seroprotected titer, which was statistically significant ($P \leq 0.05$) [12]. Manna et al. (1992) showed that response to HBV vaccination was lower in NS than in normal children. These findings are consistent with ours [13].

In the present study, the mean anti-HBs titer was significantly lower in the case group than in the control group. Similar findings were found in other studies by Neupane et al. (2019) and Manna et al. (1992) [12, 13]. In this study, the mean antibody titer was significantly ($P \leq 0.05$) lower in relapse cases than in cases with first attack. Thus, relapse cases of NS are at an increased risk of having HBV infection.

There are limited studies about the seroprotection status of NS patients against HBV vaccination. All studies have shown that the seroprotection rate was lower in NS patients. The mean titer was also lower in NS patients. Hence, NS patients have an increased risk of acquiring HBV infection.

Conclusions

Significantly lower level of anti-HBs titer is observed in NS patients compared to controls. Thus, these patients might be a potential source of HBV infection in the future in spite of vaccination. NS patients may be vaccinated during alternate days of prednisolone therapy with a double dose.

Ethical Considerations

Compliance with ethical guidelines

Ethical clearance was obtained from the Institutional Review Board of the Institute of Child & Mother Health (Code: ICMH/IRB-04NOV2020/07).

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

Conceptualization: MAA, MDH, WK; Methodology: MAA, MDH; Software: MAA, MDH, WK; Validation: MAA, MDH; Formal analysis: MAA, MDH, MAA(2); Investigation: MAA, KZ; Resources: MAA, WK, KZ, MAS; data curation: MAA, KZ, MA; Writing and preparation of the original draft: MAA, MDH, MAA(2); Writing, review, and editing: MAA, MDH, WK, MAA(2), KZ, MAS; Visualization: MAA, KZ, MAS; Supervision: MDH, WK; Project administration: MDH.

Conflict of interest

The authors declared no conflict of interests.

Acknowledgments

The authors are grateful to the participating families of the concerned subjects and express their deepest gratitude to the Department of Pathology of ICMH and the Department of Virology, BSMMU.

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