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# Evaluation of S Gene Mutations in Children with Maternally Transmitted Hepatitis B

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**ABSTRACT**

**Background & Objective:** Since the distribution of HBV genotypes in patients with hepatitis B indicates the predominant genotypes in specific geographical area, this study aimed to investigate the prevalence of S gene mutations in high-risk children with maternal HBV in southeastern Iran.

**Materials & Methods:** This cross-sectional prospective study was performed from March 2019 to March 2020**.** We studied 26 patients infected with hepatitis B virus through vertical route. Serological markers of HBV were tested for HBs Ag, anti-HBs, HBe Ag, anti-HBe, and anti-HBc through ELISA**.** HBV-positive DNA-HBV samples were examined by nested PCR**.** The correlation between categorical variables was estimated using Spearmen correlation coefficient. All statistical analyses were performed using SPSS version 22 software.

**Results:** Our study showed that no S gene mutation occurred in studied children. However, 4 (15.4%) of the children were HBe Ag positive, while the frequency of positive HBe antibody positive in the serum of children was 18 (69.2%).

**Conclusion:** In general, since different types of Pre-S / S variants are predominantly identified in patients with chronic HBV that can affect the progression of liver disease, it is therefore necessary to evaluate the types of Pre-S / S variants regularly in HBV. Carriers should be identified to help discover people at higher risk for liver disease. Our study, as a single center study in southeastern Iran, indicated no mutation in this gene in hepatitis B patients.

**Keywords:** Mutation, Hepatitis B, HBV, Children



## Introduction

There are several theories about the possible mechanisms for failure to detect HBs Ag in the presence of HBV viremia at the serum level, including reduced viral load, insufficient sensitivity of existing tests to detect HBs Ag, and mutations in the S region of the virus genome (1). In HBV infection, the cellular and humoral immune systems, naturally, act against virus-specific proteins, clearing the virus, while HBV virus, S mutations escape detection by the immune system and cause chronic liver disease that can progress to liver failure and carcinoma. Besides, these mutations can be transmitted to other people and cause the spread of HBV infection (2, 3).

The pre-S1/S2/S ORFs encode S protein(S domain) which is detected as HBsAg (4).

HBsAg is a surface protein composed of 226 amino acids, where the position of the amino acid between 99 and 169 is called the major hydrophilic region (MHR), on which the "a" determinant is located (4, 5). Mutations that alter the "a" determinant can affect the antigenicity of HBs Ag, which is thought to be essential for the development of protective antibodies and is responsible for escaping vaccine-induced immunity, evading anti-HBV immunoglobulin treatment, and generally presenting false results in serological tests (6, 7). Thus, the emergence of mutations at "a" determinant level of S protein may lead to the production of modified S protein, which, if not detected by anti-HBs antibodies, a significant role in infection has caused by the virus. Besides, S mutations may be followed by imbalances in protein synthesis and intracellular production and accumulation, resulting in direct cytopathic effects and progression of liver damage; as various studies link these mutations to disease progression and long-term consequences. Therefore,

HBV has been shown to be very important and necessary for patients with chronic hepatitis B to be screened for pre-S / S mutated infection (8, 9). In general, different types of mutations have been identified in HBV S proteins that could potentially affect in vitro antigen detection, immune response detection, HBV infection, and virion morphogenesis (10-12). According to the above findings, escape mutants with mutations in the S gene are a significant risk to the community because Hepatitis B immunoglobulin and vaccines are not effective in preventing infection (13). Numerous studies have shown that HBV in children occurs due to the failure of vaccination through vertical transmission (14). Identification of HBV mutant variants is important because of the ability of these mutants to escape detection by the host immune system, increasing virulence and resistance to antiviral drugs, facilitating binding and penetration to liver cells, and failure to detect HbsAg in routine laboratory tests (15). Since the distribution of HBV genotypes in patients with hepatitis B indicates the predominant genotypes in specific geographical area (8), this study aimed to investigate the prevalence of S gene mutations in high-risk children with maternal HBV in southeastern Iran.

## Materials and Methods

This cross-sectional prospective study was performed from March 2019 to March 2020 in Pediatric Gastroenterology Clinic of Amir-Al-Momenin Hospital in Zabol, Sistan and Baluchestan province, Iran.

### Study Population

We included 26 patients infected with hepatitis B virus through vertical pathway and investigated the S gene mutation status. This project was approved by the ethics committee of Zabol University of Medical Sciences (IR.ZBMU.REC.1398.197). All subjects and/or their families who participated in this study signed an informed consent prior to the enrollment in the study. Chronic HBV infection was diagnosed by the repeated detection of HBsAg over a period of 6 months. The sample size was estimated using the Cochrane formula according to Pourkarim et al. (16). The inclusion criteria were children with HBV born to HBs Ag-positive mothers, filling out the consent form by the parents and no other viral infections including EBV, HIV and HCV. And, the exclusion criteria were as follows: parental dissatisfaction, on-HBs Ag positive mother, liver disease and other viral infections.

### Biochemical tests

Serological markers of HBV Serum were tested for HBsAg, anti-HBs, HBeAg, anti-HBe, and anti-HBc using ELISA kits.To investigate latent hepatitis infection, DNA-HBV was extracted from all samples using DNA extraction kit (DNA, High Pure Viral Nucleic Acid kit) and then by Real Time PCR using Partus HBV RG PCR-Kit and 3000 Real Time Thermal device. Cycler Rotoe-Gen was quantified. Analytical detection limit of this kit was 20 IU / ml.

### DNA Amplification

HBV-positive DNA-HBV samples were examined by Nested PCR on 585 bp region of the S gene from the HBV genome with one pair of external primers and one pair of internal primers.

External primers were as follows:

PrsS2 (Forward, nt 2820-2837, 5'-GGGACACCATATTCTTGG-3')

SiR (reverse, nt 824-821, 5'-TTAGGGTTTAAATGTATA'CCCA)

Internal primers were as follows:

HBS1 (forward, nt 221-223, 5' -GCGGGGTTTTTCTTGTTGA-3')

TS2 (reverse, nt 787-767, 5'-GGGACTCAAGATGTTGTACAG-3')

Nested PCR was used to amplify a 633 bp fragment from nucleotides 155 to 787 of the hepatitis B virus gene. PCR products were then purified by the mentioned kit, prepared and sent for sequencing. The sequences obtained after the initial editing were edited by Chromas in DNA Star and Bioedit compared to the primer sequences. Samples were compared using Mega, Bioedit and Clastal W software. Phylogenetic analysis was performed using TREECON software. Genetic distances were estimated using the Kimura 2 parameter matrix method with the TREECON program and the phylogenetic tree was mapped using the Neighbor-joining method with the TREECON program. Bootstrap Resampling was performed with 1000 replicates to prove the validity of the phylogenetic tree.

Demographicand anthropometric data, and other laboratory tests such as liver enzymes (AST, ALT, alkaline phosphatase), direct bilirubin, total bilirubin, albumin and total protein were analyzed.

### Statistical analysis

The correlation between categorical variables was estimated using Spearmen correlation coefficient. All statistical analyses were performed using SPSS version 22 software. Age, liver enzyme, and other demographic information were expressed as mean ± standard deviation. The Chi square test and Fisher's exact test were used to compare categorical data. The significance level was set at $p<0.05$. The prognostic value was expressed as corresponding 95% confidence interval (CI).

## Results

In the present study, 26 HBV- infected patients with hepatitis B were investigated. Of these patients, 18 (69.2%) were male and mean (standard deviation) of the patients' age was 10.98(6.35) years. The youngest and oldest patients were 1 and 26 years old respectively. Also, the mean (standard deviation) age of patients' mothers was 40.45(10) years. And youngest and oldest mothers were 27 and 63 years old respectively.

The results of our study showed that no S gene mutation occurred in studied children. However, 4 (15.4%) of the children were HBe Ag positive, while the frequency of positive HBe antibody positive in the serum of children was 18 (69.2%). In this study, the prevalence rates of HBe Ag positive in HBe Ab positive and negative patients were 5% and 37.5%, respectively. In this study, 20% of the boys were HBe Ag positive, while none of the girls were HBe Ag positive. However, the frequency rates of HBe Ag and HBe Ab in different sexes were not statistically significant.

Table 1 shows that the frequency of positive HBe Ag in children with and without a history of vaccination was not different. However, the frequency of positive HBe Ag in children who had no history of vaccination was significantly higher than in children who had a history of vaccination ($p = 0.001$). Also, high viral load in children with hepatitis B was not associated with positive or negative HBe Ag and HBe Ab ($p > 0.99$).

**Table 1. Comparison of demographic information, viral load and vaccination status regarding serum HBeAg and HBeAb levels in children with hepatitis.**

| Variables | | HBeAg + | HBeAg - | P value[a] | HBeAb+ | HBeAb- | P value[a] |
|---|---|---|---|---|---|---|---|
| **Age(years)*** | | 8.50± 7.32 | 11.43±6.24 | 0.407 | 11.19±5.74 | 10.50±7.98 | 0.531 |
| **Gender°** | Male | 4(20) | 16(80) | 0.277 | 12(66.66) | 6(33.33) | 0.671 |
| | Female | 0(0) | 8(100) | | 6(75) | 2(25) | |
| **Viral load°** | Lower | 3(13.04) | 20(86.95) | >0.99 | 14(66.66) | 7(33.33) | >0.99 |
| | Upper | 1(20) | 4(80) | | 4(80) | 1(20) | |
| **Vaccination°** | Yes | 2(40) | 3(60) | 0.155 | 0(0) | 5(100) | 0.001 |
| | No | 2(9.5) | 19(90.50) | | 18(85.71) | 3(14.28) | |

***Variables are expressed as Mean ± SD, ° Variables are expressed as Count(%), [a] One way Anova for continuous data, chi square and fisher exact test for categorical data.**

Examination of patients' liver enzymes showed that the mean serum ALT in HBe Ab positive children was significantly higher than in HBe Ab negative children ($p = 0.018$) (Table 2).

**Table 2. Comparison of liver laboratory findings of children with hepatitis B in association with serum levels of HBeAg and HBeAb.**

| Variables | HBeAg + | HBeAg - | P value[a] | HBeAb+ | HBeAb- | P value[a] |
|---|---|---|---|---|---|---|
| **Ast*** | 18.75±5.67 | 15±6.96 | 0.069 | 15.55±7.64 | 15.65±4.89 | 0.981 |
| **Alt** | 14±3.36 | 15.13±6.70 | 0.99 | 17±6.42 | 10.87±3.22 | 0.018 |
| **Alk Phosphatase** | 375.50±197.38 | 373.86±215.65 | 0.989 | 343.77 ± 217.30 | 435.62±187.86 | 0.461 |

| Variables | | HBeAg + | HBeAg - | P value[a] | HBeAb+ | HBeAb- | P value[a] |
|---|---|---|---|---|---|---|---|
| Bilirubin | Direct | 0.25±0.05 | 0.23±0.07 | 0.811 | 0.23±0.08 | 0.23±0.05 | 0.879 |
| | Total | 0.65±0.25 | 1.33±0.52 | 0.091 | 0.92±0.43 | 1.35±0.61 | 0.080 |
| Alb | | 4.57±0.63 | 5.35±1.40 | 0.296 | 5.52±1.25 | 4.57±1.35 | 0.115 |
| Total protein | | 7.77±0.57 | 8.21±0.73 | 0.268 | 8.19±0.59 | 8.05±0.99 | 0.567 |

However, other laboratory findings of the patients had no significant relationship with the serum levels of HBe Ag and HBe Ab.

Pearson correlation test showed that there was no significant correlation between the duration of maternal hepatitis B and the age of the children (p = 0.99, r = 0.00) (Table 3).

**Table 3. Relationship between maternal hepatitis B infection age and the age of children when they were infected.**

| Variables | Mean ± SD | R | p-value |
|---|---|---|---|
| Age(years) | 10.98 ±6.35 | | |
| Duration of the mother's infection | 7.42±5.58 | 0.00 | 0.99 |

## Discussion

The presence of HBs negativity is not sufficient for complete removal of HBV DNA, although the results of some studies have shown that the prevalence of occult HBV infection (isolation of HBV DNA by PCR among patients with HBsAg negative) in vaccinated children born to HBsAg positive mothers is relatively high. Thus, it is necessary to consider the occult HBV Infection, especially in hypo-endemic regions and it seems that anti-HBs and HBsAg are not effective tools for diagnosing HBV infection in high-risk populations, and investigation of HBIG escape mutations is necessary (17). Occult HBV infection has also been reported in children vaccinated in Taiwan (18). Indeed, there have been many recent reports of the presence of HBV genotypes in specific geographical areas, with genome diversity being particularly related to geographical distribution, treatment resistance, and clinical characteristics. Mutations in the HBV S gene (coding gene for surface protein, or HBsAg) have been reported worldwide, but are mainly seen in Asia and are clinically significant (19). Our study focuses on the prevalence of S gene mutations in "a" determinant region among selected high-risk groups of children born to HBsAg-positive mothers in regions with moderate to high HBV prevalence and the role of these mutations in transmitting hepatitis B from HBsAg-positive mothers to the offspring. In the present cross-sectional study, serum samples of 26 HBs Ag positive children were examined. In the study population, all patients had chronic infections and were carriers, of whom only 4(15.38%) had serological evidence of active infection in the virus replication phase (HBe Ag positive).

HBe Ag is an important serum marker for HBV and is associated with higher levels of viremia increased risk of infectivity to others, and increased risk of hepatocellular carcinoma. Bisceglie et al., (20) in their study reported the prevalence of HBe Ag in the adult population and children 37%. In general, evidence suggests that Asians have the highest prevalence of HBe Ag in the second and third decades of life (21).

Many theories have been proposed regarding the occurrence of S gene mutations where most studies have associated the occurrence of various types of S gene mutations with the effect of host-induced immune stress, hepatitis B vaccination, and immunoglobulin injection (22).

Some studies have shown that the mutation frequency of HBV, especially mutations in the HBVAg coding region, is significantly higher in children with failed combined vaccination than in children who did

not receive the combined vaccination (23-25). Screening for HBV mutations in the Vaccinated Carriers in Singapore showed that 39% of the patients studied, had mutations in "a" determinant (26). Similar studies in Taiwan showed that the prevalence of HBV mutated infection after vaccination was about 22% (27, 28). Also, in a study by Lee et al., In Taipei, mutations in "a" determinant were observed in 6 (22%) vaccinated patients (29).

Moradi et al., also reported a prevalence of S gene mutation in a determinant of 12.5% in a study of children with hepatitis B in the Golestan region of Iran (13). The results of a study, contrary to the above, indicate that HBV mutations are spontaneous and unrelated to vaccination so that no significant differences are found between children with or without vaccination at the mutation sites of the "a" antigenic determinant cluster of the HBV S gene (30).

In the present study, both unvaccinated children (80.76%) and patients with a history of vaccination (19.23%) were studied. Findings of our study showed that S genome mutation has no role in hepatitis B infection in children with maternalt hepatitis B in Sistan region, so that S gene mutation was not found in any of the children studied. The results of this study were consistent with the study of Basuni et al., (30) who studied the relationship between HBsAg mutations and hpatitis B infant immunization. In this study, no "a" determinant of vaccine escape mutants were found, and vaccine escape variants were proposed as a non-effective factor for failure to prevent HBV transmission. In general, the results of the above studies indicate that HBV Pre-S / S gene mutations are common and can occur before or after vaccination. Vaccination- failure factors include high HBV DNA load in the mother and HBV gene mutations, especially the S (pre-S and S) gene (14, 31-33). Failure to identify S gene mutations in the present study compared to other studies can be related to the size, type of population, and endemicity of HBV in the study population. Voluntary participation in screening programs also leads to bias.

## Conclusion

In general, since different types of Pre-S / S variants are predominantly identified in patients with chronic HBV that can affect the progression of liver disease, it is, therefore, necessary to evaluate the types of Pre-S / S variants regularly in HBV. Carriers should be identified to help discover people at higher risk for liver disease. Our study, as a single center study in southeastern Iran, indicated no mutation in this gene in hepatitis B patients.

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## Conflict of Interest

The authors declare no conflict of interest regarding the publication of this article. The authors gave their consent for publication in this journal.

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