Serological Features of Children Vertically Infected With Hepatitis B Virus: A Study in Amir Al-Momenin Ali Hospital of Zabol

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Abstract

Introduction: Hepatitis B is a common viral infection worldwide and the main cause of chronic hepatitis, cirrhosis and liver cell carcinoma. hepatitis B e-antigen (HBeAg) is one of the markers indicating chronic hepatitis B infection. In this cross-sectional study, we investigate serological markers and HBeAg positivity in children with maternally transmitted hepatitis B virus (HBV).

Materials and Methods: Overall, 26 children with congenital HBV referred to Amir Al-Momenin Ali hospital in Zabol in 2019 and 2020 were enrolled. After gathering demographic characteristics, blood samples were taken from the patients. Serological tests were performed by routine ELISA tests. Data were analyzed using SPSS software version 22.

Results: Twenty-six children were included in the study; 18 of them (69.2%) were males. The mean age of the participants was 13.98 ± 11 years (minimum of 1 and maximum of 18 years old). The mean age of mothers was 40.45 ± 10 years (minimum of 27 and maximum of 63 years old). Four (15.4%) of the children were HBeAg positive, and 18 (69.2%) were HBeAb positive with no significant differences between genders ($P > 0.05$). HBeAg positivity was not associated with the birth rank ($P = 0.71$) or HBV vaccination ($P = 0.17$). Liver enzymes, serum albumin and children's age and duration of maternal infection were not significantly different between HBeAg positive and HBeAg negative groups ($P > 0.05$). Mean serum alanine transaminase (ALT) was significantly higher in HBeAb positive than HBeAb negative children ($P = 0.018$), and HBeAb positivity was significantly associated with HBV vaccination history ($P = 0.02$). Other liver enzymes as well as age of mother and child and the duration of maternal infection were not significantly different between the two groups ($P > 0.99$).

Conclusion: The prevalence of chronic HBV infection based on HBeAg positivity was relatively high in children vertically infected with the virus. HBeAb seroconversion seems to be associated with HBV vaccination.

Keywords: Hepatitis B virus, Vertical infection, Aminotransferases, Vaccination

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Introduction

Hepatitis B virus (HBV) is common infection afflicting more than 2 billion people around the world. Among these, around 3500 million (a total of 5% of the global population) have been identified as carriers,^{1,2} and 75% of these carriers reside in the western Pacific region and Asia.^{3,4} Hepatitis B infection frequency in Iran varies between 17% and more than 50% between different provinces.⁵ It has been mentioned that more than a third of Iranians have been exposed to HBV, and

about 3% of them are chronic carriers, the lowest of which has been reported in Fars province (2.7%) and the highest in Sistan and Baluchestan (5%).⁶

Mother-to-child (vertical) transmission (MTCT) is one of the most important ways through which HBV is transmitted. This method of transmission may occur through the placenta, during labor, or shortly thereafter.⁷ More than 50% of Iranian carriers received the infection from their mothers, which is one of the most likely routes of HBV transmission in our

country.⁵ Maternally infected children are 25 percent more likely than others to develop cirrhotic liver cancer.⁸ Among most important predictors of MTCT are HBV DNA status, as well as serological status for hepatitis B e-antigen (HBeAg) and HBeAb.⁹ Children who acquire HBV prenatally have a high chance for developing chronic and persistent disease. In these children, seroconversion of HBeAg to HBeAb is an important marker indicating the inactivation of virus replication; in case of this phenomenon is not seen, patients will need a continuation of antiviral therapy.¹⁰ The rate of elimination of HBeAg, with or without HBeAb positivity, is seen in a relatively low ratio of patients.¹¹

Due to the high prevalence of hepatitis B in Sistan and Baluchestan province of Iran, and the fact that HBV clinical course is largely unknown in children with maternally transmitted HBV, we here decided to evaluate the status of HBeAg and HBeAb in these children before the age of 18 years old.

Patients and Methods

This cross-sectional study was performed on 26 children (<18 years old) born with congenital HBV infection (HBsAg positivity at birth) in the Amir-Al-Momenin hospital of Zabol city. After obtaining an informed consent from parents and completing a questionnaire for demographic characteristics, blood samples were taken from children.

Laboratory tests including aspartate aminotransferase (AST), alanine transaminase (ALT), HBeAg, HBeAb, HBsAg, alkaline phosphatase (ALP), albumin, bilirubin total, bilirubin direct, and total protein were determined for all children using specific ELISA kits. Data was analyzed using SPSS software version 22 using the chi-square test and independent sample student *t* test at the significance level of $P < 0.05$.

Results

Twenty-six children were included in this study; 18 of them (69.2%) were males. All these children had positive HBsAg test at birth. The mean age of the children was 10.98 ± 6.35 years. The youngest and oldest were 1 and 18 years old, respectively. The mean age of the mothers was 40.45 ± 10 years (the range of 27 to 63 years). Half of the

children (52%) were the second child of the family. Table 1 shows laboratory parameters in the studied children.

Table 2 shows that 4 (15.4%) of the children were HBeAg positive. The frequency of HBeAb positivity was 18 (69.2%).

Overall, 20% of boys and 0% of girls were HBeAg positive; however, the difference between the two sexes was not statistically significant ($P > 0.05$) (Table 3). HBeAg positivity was not associated with the birth rank or HBV vaccination ($P = 0.155$). Also, liver enzymes, serum albumin, patient's age, and duration of maternal infection were not significantly different between the two groups ($P > 0.05$).

Table 4 shows that HBeAb positivity was not significantly associated with a history of labor bleeding, gender, or birth rank. However, the frequency of HBeAg positivity was significantly higher in children without a history of HBV vaccination ($P = 0.001$). Furthermore, the mean serum ALT was significantly higher in HBeAb positive than negative children ($P = 0.018$). Other liver enzymes as well as patients' and mother ages, and duration of maternal infection were not significantly different between the two groups.

Discussion

In the present study, out of 26 children aged <18 years old born to HBsAg positive mothers, 4 (15.4%) were HBeAg positive, and 18 (69.2%) were HBeAb positive. All the children were HBsAg positive at birth. HBeAg positivity was not associated with the birth rank or HBV vaccination ($P = 0.155$), but the mean of serum total bilirubin was significantly lower in HBeAg positive patients than in HBeAg negative ones (0.65 vs 1.07 , $P = 0.019$). However, liver enzymes, serum albumin, patient age, and duration of maternal infection were not significantly different between the two groups ($P > 0.05$).

In a study in Taiwan, the prevalence of the children

Table 2. HBeAg and HBeAb Status in the Studied Children

Serological Variables		HBeAb		<i>P</i>
		Positive	Negative	
HBeAg	Positive	1 (5)	3 (37.5)	0.072
	Negative	17 (95)	5 (62.5)	

Table 1. Laboratory Parameters in the Studied Children

Variables	Mean (SD)	Median	Minimum	Maximum
AST (IU/L)	15.57 (6.81)	14	9	33
ALT (IU/L)	15.11 (6.26)	14.5	8	30
ALP (IU/L)	374.11 (209.14)	353.5	120	727
Direct Bilirubin (mg/dL)	0.23 (0.07)	0.25	0.10	0.30
Total Bilirubin (mg/dL)	1.05 (0.52)	0.90	0.30	2
Albumin (mg/dL)	5.23 (1.33)	4.95	3.29	8.60
Total protein (mg/dL)	8.15 (0.72)	8.15	7.10	9.50

Table 3. HBeAg Status and its Association with Laboratory and Clinical Parameters

Variables		HBeAg		P
		Positive (n=4)	Negative (n=22)	
Child's age (y)		8.5±7.32	11.43±6.24	0.40
Mother's age (y)		38±11.69	41±9.89	0.6
AST (IU/L)		18.75±5.67	15±6.96	0.06
ALT (IU/L)		14±3.36	15.13±6.7	0.9
ALP (IU/L)		375.5±198.38	373.86±215.65	0.98
Direct bilirubin (mg/dL)		0.25±0.05	0.23±0.07	0.81
Total bilirubin (mg/dL)		0.65±0.25	1.13±0.52	0.091
Albumin (mg/dL)		4.57±0.63	5.35±1.40	0.29
Total protein (mg/dL)		7.77±0.57	8.21±0.73	0.26
HBV vaccination	Yes	2 (50)	15 (68.1)	0.17*
	No	2 (50)	7 (31.9)	
Birth rank	1 st	2 (50)	6 (27.2)	0.71
	2 nd	2 (50)	14 (63.6)	
	4 th	0 (0)	2 (9.2)	

Data are expressed as mean±SD or No. (%).

* Fisher's exact test

Table 4. HBeAb Status and its Association With Laboratory and Clinical Parameters

Variables		HBeAb		P
		Positive (n=18)	Negative (n=8)	
Child's age (y)		11.19±5.74	10.5±7.98	0.53
Mother's age (y)		41.66±10.07	37.85±10.1	0.53
AST (IU/L)		15.55±7.64	15.65±4.89	0.98
ALT (IU/L)		17±6.42	10.87±3.22	0.018
ALP (IU/L)		343.77±217.30	435.62±187.86	0.46
Direct bilirubin (mg/dL)		0.23±0.08	0.23±0.05	0.87
Total bilirubin (mg/dL)		0.92±0.43	1.35±0.61	0.08
Albumin (mg/dL)		5.52±1.25	4.57±1.35	0.11
Total protein (mg/dL)		8.19±0.59	8.05±0.99	0.56
HBV vaccination	Yes	12 (66.6)	5 (62.5)	0.02*
	No	6 (33.4)	3 (37.5)	
Birth rank	1 st	5 (27.7)	3 (37.5)	0.74
	2 nd	11 (61.1)	5 (62.5)	
	4 th	2 (11.2)	0 (0)	

* Fischer exact test.

Data are expressed as mean±SD or No. (%).

carrying HBsAg, who born to HBsAg-positive mothers, was reported to be 2.4%.¹² In two reports in China, these rates were reported as 7.2% and 13.7%.^{13,14} Another study by Zhu in China found that 14.7% of these children carried HBsAg.¹⁵ These evidence shows that vertical transmission of HBV infection is a serious health concern among societies, and those infected with the virus via this route must be under close clinical surveillance. In the present study, we focused on the chronicity of HBV infection in children who acquired the virus from their mothers and

were HBs Ag positive at birth.

In a study in Senegal, of 10 infants who born with a positive HBs Ag status, 5 showed either anti-HBs, HBc, or HBe antibodies after 6 months.¹⁶ In another study in Japan on children with MTCT HBV infection, the seroconversion of HBeAg at the ages of 3 and 15 years was shown to be 26% and 42%, respectively.¹⁷ The recent study indicates a higher rate of seroconversion with aging of children. Consistent with this, we here observed the mean ages of 8.5±7.32 and 11.43±6.24 in HBeAg positive

and negative patients, respectively. Although the age difference was not statistically significant, which may be due to the low number ($n=4$) of HBeAg positive cases, this indicates that there is a tendency toward HBeAg seroconversion with age.

Nevertheless, the rate of HBeAg seroconversion to HBeAb seems to be under the influence of multiple factors. This seems to be lower in children infected with HBV genotype C.¹⁷ In one study; however, genotype B was more commonly associated with both HBeAg and HBeAb positivity in children.¹⁸ Nonetheless, genotype C was still an independent risk factor for delayed HBeAg seroconversion.¹⁸ Despite the use of immunoprophylaxis, infants who became chronically infected with HBV may be infected in the womb, or the mother may have a high load of the virus, or the baby may have mutated viruses. Vaccine-escape virus mutants^{19,20} and HBeAg positivity in mothers²¹ were also found to be associated with chronic HBV infections in descendants. In fact, it has been noted that passing through an immune clearance phase and the appearance of HBeAbs can be delayed by core and pre-core mutations in HBV genome.^{22,23} HBV viruses transmitted within a family have shown a higher rate of core and pre-core mutations at HBeAg clearance phase, probably due to interactions of the same virus strain with immune systems of multiple hosts.²⁴ We here did not find any significant association between HBeAg positivity and parameters such gender, birth rank, or a history of HBV vaccination.

According to our study, HBeAb positivity was significantly higher in children with a history of HBV vaccination. Vaccination is a standard health care procedure for infants born from HBV infected mothers.²⁵ Passive and active immunization of infants born to HBsAg-positive mothers is the most important and effective way to prevent perinatal transmission of HBV infection.^{19,20,26} The number of carriers among descendants is a good candidate to evaluate the effectiveness of the vaccination program. Studies in Taiwan and Hong Kong showed that the effect of the vaccine alone was significantly more pronounced, especially when the mother is HBeAg positive.^{27,28} We here reported that a history of vaccination may help to achieve immunity by promoting HBeAb production.

In the present study, HBeAg positive children here also had higher AST than HBeAg negative ones (18.75 ± 5.6 vs 15 ± 6.9); however, this was statistically insignificant. On the other hand, ALT showed no significant difference between the two groups. An elevated ALT in these patients was better predicted by HBeAg status as patients with a positive HBeAg test are more likely to have abnormal ALT.²⁹ Regarding HBeAb status, we noticed a significantly higher ALT level in those with a positive anti-HBeAg test (17 ± 3.22 vs 10.87 ± 3.22 , $P=0.01$). This suggests that HBeAb seroconversion may not accurately predict the

clinical condition at immune clearance phase, and the fact that HBV carriers may still suffer from some degrees of hepatic injury under the influence of other parameters.²⁹ In previous studies, it was shown that 29 to 65% of HBeAb positive carriers still had variable degrees of HBV DNA.^{29,30} Genotype D of HBV, especially strains with core and pre-core mutations, can independently predict elevated ALT in HBeAb positive patients.²⁹ Patients with anti-HBeAb in their serum can still show degrees of hepatic injuries such as inflammation and necrosis.³⁰

Some parameters regarding mothers' status of HBV infection (e.g., HBV DNA level, HBeAb titer, HBV DNA mutations) were not studied before and during pregnancy. Also, it is better to check HBV DNA mutations, virus strains, and histological parameters in vertically infected children with chronic infection to be able to better predict their clinical course.

Conclusion

Chronic HBV infection in vertically infected children was relatively high. Various parameters (either mother or child related) may influence HBeAg seroconversion in these children. Although there were no significant differences between the children regarding clinical course of the disease, it is advisable to monitor these children with chronic infection for possible hepatic injuries.

Authors' contributions:

IS: Concept, supervision, critically revising the manuscript; AM: concept, design; PO, MS, HM, and AKB: data collection; AB: Drafting the manuscript, statistical analysis.

Ethical Approval

The study was approved by the ethics committee of Zabol University of Medical Sciences (IR.ZBMU.REC.1398.197).

Competing Interests

The authors have no conflict of interest to declare.

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