

Original Article

## Risk factors associated with horizontal transmission of hepatitis B viral infection from parents to children in Mexico

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### Abstract

**Introduction:** Hepatitis B virus (HBV) infection in children is a health problem worldwide. In Mexico, a high prevalence rate of HBV infection and occult HBV infection have been reported in high-risk adults and children. However, studies regarding HBV infection transmitted from HBV-infected parents to children are limited. This study aimed to determine the risk factors associated with HBV transmission of HBV from parents to children in Mexico.

**Methodology:** A retrospective case-control study was carried out in 24 pediatric patients with clinical HBV infection and 48 healthy controls. Bivariate and forward conditional logistic regression analysis was used to compare demographic variables, the status of HBV vaccination, and risk factors for HBV infection transmission among children and their parents.

**Results:** No newborns were diagnosed with HBV infection, and no significant differences were found in age ( $p = 0.209$ ) or gender ( $p = 0.612$ ) compared to the control group. The independent risk factor associated with HBV transmission was the presence of a parent with a history of promiscuity (OR = 30.95, 95%CI = 3.382-283.326;  $p = 0.002$ ), whereas having completed the HBV vaccination schedule for their age was a protective factor against HBV infection in the children (OR = 0.245, 95%CI = 0.079-0.764;  $p = 0.015$ ).

**Conclusions:** HBV infection in Mexican children is associated with close interpersonal contact with a parent engaged in high-risk sexual practices suggesting that the horizontal route could be the primary mode of infection. Child and adult vaccination campaigns should be reinforced to avoid HBV infection in Mexico.

**Key words:** Horizontal transmission; vaccination; occult hepatitis B; Latin America; risk factors; pediatrics.

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### Introduction

Pediatric hepatitis B virus (HBV) infection is an important public health problem worldwide [1,2]. HBV infection in children is a primary cause of chronic HBV infection in adulthood. In fact, 80% to 90% of infants who are infected within the first year of age develop chronic HBV infection before the age of six. In contrast, chronicity occurs in less than 5% of older children and adults [3]. Furthermore, children who are not HBV vaccinated are also vulnerable. Thus, identifying the risk factors and related routes of transmission is crucial to prevent and decrease the risk of pediatric HBV infection and chronic liver disease.

The knowledge about risk factors for pediatric HBV infection has been mainly documented from Asia and

Africa that have higher endemicity rates due to perinatal HBV transmission and distinct genotypes [1]. In these regions, HBV infections in children co-infected with human immunodeficiency virus [4], living with an HBsAg-positive parent [5] or exposed to multiple transfusions [6,7] have been reported. Furthermore, in countries with intermediate HBV prevalence, the lack of HBV vaccination is the most frequent risk factor in HBV-infected children [8]. However, data regarding the risk factors in children with suspected HBV infection is limited in countries with a low HBV prevalence.

In Latin America, the HBsAg prevalence of the general population ranges from < 2% to 7%. Mexico is classified as a low endemic country (< 2%) by the

World Health Organization [3]. However, HBV infection is the third cause of viral hepatitis, and its epidemiological features are based on the predominance of HBV genotypes H and G [9-10]. Although the prevalence rate of HBsAg is < 0.3% among adults [11], the rates of HBsAg and the anti-HBc antibody can rise up to 16.5% and 30.2%, respectively in risk groups with low socioeconomic status [12] and occult HBV infection ranges from 11.32% to 18.4% [9,13,14]. HBV infections are frequent in adults between 25 and 44 years of age [15]. In pregnant women, HBsAg prevalence ranges from 0.93% to 2.52% suggesting that young children could be exposed to HBV [11]. In recent studies, an HBsAg prevalence of 3.1% among Mexican children was reported [16], and a high prevalence of occult HBV infection (87.5%) was detected [17].

Among Mexican adults, horizontal transmission by percutaneous exposure, high-risk sexual practices, and parenteral transfusions is common, whereas injection drug use may be an emerging route [9-12]. Recently, a high frequency of HBV risk factors in parents of HBV-infected children was reported [17]. However, the association of the risk factors in Mexican children who are positive for HBV-DNA and their parent's risk factors as well as the plausible route of transmission of HBV infection in children have not been thoroughly evaluated. Therefore, this study aimed to determine the risk factors associated with HBV transmission of HBV from parents to children in Mexico.

## Methodology

### *Study design and population*

A case-control study was conducted to evaluate the risk factors for HBV transmission among HBV-infected Mexican children and their parents at the Department of Molecular Biology in Medicine, Civil Hospital of Guadalajara, "Fray Antonio Alcalde." The study period was from January 2015 to December 2016. Twenty-four cases diagnosed with HBV infection by serological and molecular tests from a previous cohort of 215 children were included [17]. Briefly, the status of infection of these 24 patients was occult HBV infection (HBV-DNA positive/HBsAg negative) in 87.5%, (n = 21/24) of the cases and 12.5% (n = 3/24) were positive for both markers. HBV genotype H was prevalent in 71% (n = 17/24) of the children, followed by genotype G in 8% (n = 2/24), and genotype A in 4% (1/24). Four of the HBV cases were non-typeable of which two were HBsAg positive (2/3), and two were HBsAg negative (2/21) due to low viral load. This data was used for comparative purposes.

The control group was 48 healthy children attended at this same hospital, and they did not present clinical hepatitis nor laboratory evidence of HBV infection during the study period. Serum samples were screened for HBsAg (AxSYM HBsAg (V2), Abbott Laboratories, Chicago, IL).

### *Data collection*

A structured questionnaire was used to collect the clinical history containing demographic characteristics (age, group age, and gender), HBV vaccination, and risk factors for HBV transmission among children and their parents in both case and control groups. HBV vaccination was verified by the child's vaccination card and was considered complete if the child had a three-dose schedule at two, four, and six months of age, as recommended by the National Ministry of Health during 2000 to mid-2007.

The children and their parents (mothers and fathers) were asked about personal behavior and health care services related to risk factors for HBV infection by using a structured questionnaire. The following risk factors were recorded: a history of hospitalizations, promiscuity, history of surgery, injection or inhaled drug use, blood transfusion, tattoos, history of sex with a sex worker, contact with contaminated body fluids, accidental needle-stick, acupuncture, injections with contaminated needles and hemodialysis [16,17].

Other risk factors investigated in the children's parents were a history of hepatitis without an etiological agent, HBV infection, hepatitis C infection and a history of cirrhosis or hepatocellular carcinoma. Vaccination against HBV infection in the children's parents was considered covered if a three-dose series of HBV vaccine had been completed.

### *Statistical Analysis*

Descriptive statistics were computed to assess the individual characteristics of the cases and control groups. The data for continuous variables were reported as the mean, median, and standard deviation (SD). The demographic and clinical data were given as simple frequencies and proportions. Statistical associations were conducted by Student's *t*-test, chi-square test, or Fisher's exact test when appropriate. Bivariate analysis was performed using a chi-square test with an odds ratio (OR) calculated for risk factors. A P-value of < 0.05 was considered statistically significant, and a confidence interval was set at 95%. All risk factors with a significant OR ( $p < 0.05$ ) or those with borderline significance ( $p < 0.20$ ) were chosen for further evaluation. Logistic regression was used to analyze

**Table 1.** Comparison of Demographics of Pediatric Patients with HBV Infection and Healthy Controls.

Demographic Variable*	Patients‡	Controls	P-value†
	(n = 24)	(n = 48)	
Age (years)	6.8 ± 4.1 (1 - 15)	5.5 ± 4.1 (1 - 14)	0.209
Gender male [n, (%)]	13 (54.2)	29 (60.4)	0.612
Age group [n, (%)]			
Newborn	0 (0.0)	0 (0.0)	0.162
1 month–2 years	4 (16.7)	15 (31.3)	
3–6 years	6 (25.0)	16 (33.3)	
7–11 years	11 (45.8)	10 (20.8)	
12–15 years	3 (12.5)	7 (14.6)	

\*Demographic variables are presented as means ± SD (range), unless otherwise indicated. †P-values were calculated by Student's t test, chi square test, or Fisher's exact test. ‡Patients are the children positive for HBV-DNA. Abbreviations: SD, standard deviation.

independent risk factors for HBV infection. Two models were built using enter and conditional forward methods. The risk factors that changed the chi-square value of the model significantly were preserved to construct the final model.

### Ethics

The parents provided written, informed consent at the time of the clinical evaluation for both their children and themselves. The Institutional Ethical Committee approved this protocol, and it was conducted in accordance with the Declaration of Helsinki 1975, as revised in 1983.

### Results

Table 1 summarizes the demographic data of the study cases and the control group. The mean age of case-patients was 6.8 ± 4.1 years with a range from 1-15 years. The case subjects were predominantly male (54.2%, 13/24). No significant differences were found in the age, gender, or age-group distribution between the cases and control groups.

Table 2 shows the risk factors registered in the children's cases and controls. At least one risk factor known for HBV transmission was found in all HBV-infected children. All of the children's parents reported that their children had been exposed to at least one potential risk factor for HBV transmission. A history of HBV infection in the HBV-infected children's parents or hepatitis without a known diagnosis were significantly associated with acquiring HBV infection among these children. Of the four cases of HBV-infected children's parents, three were a father and one, a mother. HBV vaccination in the children was a protective factor for acquiring HBV infection.

Table 3 shows the risk factors in HBV-infected children's parents and the respective control group. Histories of promiscuity, illegal drug use, sex with sex worker and acupuncture were risk factors in the children's parents significantly associated with the risk of HBV infection among HBV-infected children. Histories of HBV infection or/and hepatitis without a known diagnosis among the parents were not found in the control group. Also, none of the parents of the HBV-infected children and control group were vaccinated.

**Table 2.** Bivariate Analysis of Risk Factors for HBV Infection and Hepatitis B vaccination in Mexican Children.

Variable	Cases†	Controls	Odds ratio (95%CI)	P-value*
	(N = 24) n (%)	(N = 48) n (%)		
Hospitalizations	9 (37.5)	18 (37.5)	1.000 (0.363-2.751)	1.000
Surgery	5 (20.8)	3 (6.2)	3.947 (0.856-18.202)	0.107
Tattoos	1 (4.2)	1 (2.1)	2.043 (0.122-34.157)	1.000
Blood transfusion	1 (4.2)	1 (2.1)	2.043 (0.122-34.157)	1.000
Sex with a sex worker	1 (4.2)	0 (0.0)	0.324 (0.231-0.453)	0.333
Promiscuity	1 (4.2)	0 (0.0)	0.324 (0.231-0.453)	0.333
Acupuncture	1 (4.2)	0 (0.0)	0.324 (0.231-0.453)	0.333
Injection with contaminated needles	1 (4.2)	0 (0.0)	0.324 (0.231-0.453)	0.333
Parent with hepatitis without a known diagnosis	6 (25.0)	0 (0.0)	18.05 (2.079-156.726)	0.002
Parent with history of HBV infection	4 (16.7)	0 (0.0)	11.67 (1.284-106.037)	0.016
Vaccination against HBV infection‡	9 (37.5)	33 (68.8)	0.273 (0.098-0.762)	0.011

\*P-values were calculated by chi-square test or Fisher's exact test. †Cases were the children positive for HBV-DNA. ‡Vaccination against HBV infection was considered affirmative if the child had a completed HBV vaccination schedule at 2, 4, and 6 months of age. Abbreviations: CI, confidence interval.

**Table 3.** Bivariate Analysis of the Children's Parents Risk Factors for HBV Infection and HBV vaccination.

Variable	Cases <sup>†</sup>	Controls	Odds Ratio (95% CI)	P-value*
	(N = 24) n (%)	(N = 48) n (%)		
Hospitalizations	21 (87.5)	33 (68.8)	3.18 (0.821-12.335)	0.083
Surgery	19 (79.2)	30 (62.5)	2.28 (0.725-7.168)	0.153
Promiscuity	8 (33.3)	0 (0.0)	25.94 (3.057-220.136)	0.0003
Illegal drug use	7 (29.2)	3 (6.3)	6.18 (1.430-26.678)	0.013
Tattoos	6 (25.0)	9 (18.8)	1.44 (0.446-4.674)	0.538
Sex with a sex worker	5 (20.8)	0 (0.0)	14.70 (1.662-130.039)	0.005
Acupuncture	4 (16.7)	0 (0.0)	11.67 (1.284-106.037)	0.016
Blood transfusion	4 (16.7)	4 (8.3)	2.20 (0.499-9.696)	0.427
Contact with contaminated body fluids	2 (8.3)	1 (2.1)	4.27 (0.368-49.676)	0.256
Accidental needle-stick	1 (4.2)	1 (2.1)	2.04 (0.122-34.157)	1.000
Injection with contaminated needles	1 (4.2)	0 (0.0)	4.08 (0.352-47.303)	0.268
Hemodialysis	1 (4.2)	0 (0.0)	4.08 (0.352-47.303)	0.268
Parent with hepatitis without a known diagnosis	6 (25.0)	0 (0.0)	18.05 (2.079-156.726)	0.002
Parent with history of hepatitis B infection	4 (16.7)	0 (0.0)	11.67 (1.284-106.037)	0.016
Parent with hepatitis C infection	1 (4.2)	2 (4.2)	1.00 (0.086-11.613)	1.000
Cirrhosis	1 (4.2)	7 (14.6)	0.255 (0.029-2.201)	0.255
Vaccination against HBV infection <sup>‡</sup>	0 (0.0)	0 (0.0)	1.96 (0.118-32.665)	1.000

P-values were calculated by chi-square test or Fisher's exact test. <sup>†</sup>The study cases were the parents of the children diagnosed with HBV. <sup>‡</sup>Vaccination against HBV infection was considered affirmative if the children's parents had completed a three-dose series of HBV vaccine. Abbreviations: CI, confidence interval.

Table 4 shows that a history of promiscuity in the children's parents was an independent risk factor for prediction of HBV infection in their children (adjusted OR = 30.95, 95%CI 3.382-283.326,  $p = 0.002$ ), whereas HBV vaccination was a protective factor to acquire HBV infection in these children (adjusted OR = 0.245, 95%CI 0.079-0.764,  $p = 0.015$ ).

## Discussion

Data regarding the association between risk factors and routes of transmission is limited in countries with a low prevalence of HBV infection. Herein, 24 Mexican children who had been diagnosed with HBV infection by HBV-DNA positivity (87.5% occult HBV infection) were further analyzed [17]. In this study, a history of promiscuity in the children's parents was associated with risk of HBV infection in their children ( $p = 0.002$ ). This finding is similar to reports related to risk factors for HBV infection among adults in high prevalence countries [4,8,18-21]. In contrast, no vertical mother-to-child HBV transmission seems to have occurred since

no newborns were diagnosed with HBV. Risk factors such as having a parent with HBV infection or a history of hepatitis without a known diagnosis places a child at risk for transmission of HBV have been reported in countries with intermediate to high HBV prevalence, where transmission occurs later in infancy and childhood [22-24]. In this study, the age of all HBV-infected children with clinical manifestations was older than one year. These features suggest that during infancy, the horizontal parent-to-child transmission by close contact with a parent who has HBV infection could be the most frequent route in Mexican children. Other data that supports this assumption is the fact that occult HBV infection is highly prevalent among Mexican adults [9,10,13,14], and it is commonly underdiagnosed. Furthermore, these data are consistent with two previous studies in HBV-infected pregnant Mexican women in which a low HBsAg prevalence (1.2% and 1.8%, respectively) resulted in a low rate of vertical mother-to-child HBV transmission at birth [25,26].

**Table 4.** Multivariate Analysis of the Risk Factors Associated with HBV Infection in the Children.

Variable	Crude Odds Ratio (95% CI)	Adjusted Odds Ratio <sup>†</sup> (95% CI)	P-value*
<b>Risk factor</b>			
History to have promiscuity in the children's parents	25.94 (3.057-220.136)	30.95 (3.382-283.326)	0.002
<b>Protective factor</b>			
Vaccination against HBV infection in the children	0.273 (0.098-0.762)	0.245 (0.079-0.764)	0.015

\*P-values were calculated by chi-square test, or Fisher's exact test. <sup>†</sup>The crude odds ratios for this risk factor and HBV vaccination in the children were adjusted based on the following children's parents risk factors: history to have hospitalizations, surgery, illegal drug use, sex with a sex worker, acupuncture, hepatitis without a known diagnosis, and hepatitis B infection. Abbreviations: HBV, hepatitis B virus; CI, confidence interval.

In this study, the children who received HBV vaccination were protected against the transmission of the virus ( $p = 0.015$ ); thus reducing the risk of acquiring HBV infection by 75.5%. Universal administration of the HBV vaccine in children was implemented by the National Ministry of Health in the year 2000 (with a three-dose schedule at two, four, and six months of age). Currently, the recombinant vaccine against HBV infection is given at birth, two and six months of age since 2007. However, in this study, 62.5% of the HBV-infected children did not receive HBV vaccination nor did the children's parents (cases and controls). Vaccination in adults engaged in risky behavior has proven as a protective factor against HBV infection [27]. Therefore, HBV vaccine campaigns should be a priority among unvaccinated adults, including pregnant women, adults who engage in high-risk practices or undergo invasive procedures [28].

In regards to modes of HBV transmission and HBV genotypes, mother-to-child transmission has been documented in high endemic regions of Asia where HBV genotypes B and C are predominant [1], whereas this route is less frequent with HBV genotypes A, D, and E in Europe and Africa [29]. However, these same genotypes have been transmitted horizontally in children of Senegal and Saudi Arabia [22,23]. In Mexico, HBV genotypes H and G are the most frequent followed by A and D among adults and children [9,12,17]. In a previous study, most children cases were infected with HBV genotype H [17], suggesting that it may be implicated in the horizontal route of HBV transmission in Mexican children. However, when comparing the clinical data with the distribution of HBV genotypes, (data not shown) the one case of HBV genotype A was found among a vaccinated child, and two cases with HBV genotype G were not vaccinated; in all three, none of the parents had been vaccinated. Furthermore, it is noteworthy that these families have low literacy rates, low income, and limited access to health insurance that are social vulnerabilities related to the risk of acquiring HBV infection in developing countries [21,30]. These features increase the risk of HBV infection in children regardless of the low rate of infection among the adult Mexican population [12] because they share the same impoverished environment as those who live in regions with higher endemicity. Thus, further prevention strategies are needed to avoid potential chronic infection in young children.

## Conclusions

High-risk sexual practices in the children's parents were associated with HBV infection in children. Close

contact with a parent with HBV infection and a history of hepatitis without a known diagnosis were risk factors associated with HBV transmission in children, suggesting that the horizontal route could be the main route of infection in pediatric patients in Mexico. HBV vaccination in children was protective and none of the parents in this study had been vaccinated. Child and adult vaccination campaigns should be reinforced to avoid transmission of HBV infection in Mexico.

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## Authors' contributions

GEM contributed to the initial design of the manuscript, the acquisition of the clinical data and was responsible for revising the manuscript critically for important intellectual content. AP was responsible for designing and revising the manuscript critically for important intellectual content. AC contributed to the revision of the analysis of the clinical data and was responsible for revising the manuscript critically. SR was responsible for designing, analyzing data, and revising the manuscript critically for important intellectual content. All authors contributed to writing the final version of the paper.

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