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Prevalence of hepatitis B infection and factors associated in children of Ivorian HBsAg carrier subjects

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ABSTRACT

Aims of the Study: 1) Determine the Prevalence of Hepatitis B virus (HBV) infection in children (contact subjects) of chronic Hepatitis B surface antigen (HBsAg) carrier subjects (index subjects); 2) Search for factors associated with HBV infection in these children. Patients and Methods: Retrospective-cross-sectional study (January 5th, 2006 through December 31st, 2012). Studied parameters: biological and clinical characteristics of index subjects; Prevalence of HBsAg and Hepatitis B core antibody (HBcAb) in their children. Search for the HBV infection associated factors in the children (univariate analyses through Chi-square or Fisher's exact test; multivariate analysis through a backward logistic regression). Results: Our 44 subjects' median age was 43.1 ± 7.49 years and 88.6% of them lived with a spouse. Average number of children per index subjects was 2.3 ± 1.1. Our 92 children's median age was 9.3 ± 4.55 (ranging from 1 to 15 years), and 43 (44.8%) were vaccinated against HBV. HBV infection prevalence was 24% (23/96 of which, 4 were HBsAg positive and 19 HBcAb positive subjects without HBsAg). Independent factors associated with HBV infection in children of index subjects were HBV DNA for index subjects >2000 IU/ml (OR = 11.5; p = 0.001), existence of HBV in two parents (OR = 7.9; p = 0.03) and absence of HBV vaccination in the children (OR = 30.9; p = 0.003). Conclusion: Immunization coverage for children of index subjects was insufficient, especially before the introduction of HBV vaccine into the enlarged vaccination program. Outside vertical transmission, those children were more exposed to HBV intrafamilial transmission risk when they were not immunized against HBV, when both parents were infected and when HBV viremia in index subjects was higher than 2000 IU/ml.

Keywords: Hepatitis B Infection; Intrafamilial Transmission; Screening

1. INTRODUCTION

Hepatitis B virus (HBV) infection is a real public health problem worldwide and more particularly in high prevalence areas, such as sub-Saharan Africa [1-7], because of its progressive complications (cirrhosis and hepatocellular carcinoma), comorbidity frequency (especially HIV infection) and management difficulties in the particular context of our countries with limited financial resources. In sub-Saharan Africa, both main transmission ways are vertical or perinatal and intrafamilial horizontal in early childhood [5,7]. Introduction of HBV universal immunization for newborns into enlarged vaccination programs (EVP) of our countries in Sub-Sahara dates generally from at least two decades. In most EVP of our countries, HBV immunization only starts from the 6th week after birth (pentavalent or hexavalent vaccine). Moreover, owing to anti-HBs immunoglobulins (Ig) availability problems in our countries, passive immunoprophylaxis is almost never associated with active immunization. Vertical and intrafamilial horizontal transmission risks of HBV infection remain a concern before HBV immunization, especially during children's first six weeks of life. This study aims to determine HBV infection prevalence among children (contact subjects) of hepatitis B surface antigen (HBsAg) chronic carrier subjects (index subjects) through familial screening of HBV infection and search for factors associated with HBV infection in these children.

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2. PATIENTS AND METHODS

It's about a retrospective cross-sectional study (January 5th, 2006 through December 31st, 2012). Records of HBsAg chronic carrier patients, with ambulatory follow-up in two medical centers in Abidjan (University Hospital of Yopougon and Clinique Médicale Danga), were analyzed. All the HBsAg-positive patients (index subjects), whose family surrounding (contacts subjects: spouses and children) was subjected to systematic screening for HBV infection, were included in our study (search for HBsAg and hepatitis B core antibody (HBcAb) in contact subjects: Mini Vidas®; Biomerieux, Marcy l'Etoile, France). Subjects whose children were more than 15 years old were excluded from the study.

A systematic and minimal biological checkup was realized for every index subject; the checkup included transaminases determination (Cobas® Integra 400 plus; Roche diagnostics, Mannheim, Germany), a search for HBeAg, anti-HBeAb and anti-HBcAb, anti-HCV Antibodies (Mini Vidas®; Biomerieux, Marcy l'Etoile, France), DNA HBV determination using a real-time PCR assay (Cobas® Amplicor HBV Monitor assay, threshold of detectability 35 copies/ml or 6 IU/ml; Roche Diagnostics) and HIV test (screening test using Determine® and confirmation test using Genie II®).

Main evaluation criteria was the existence of HBV infection in index subjects' children testified by presence of HBcAb. The infection was past when HBsAg was negative and present when HBsAg was positive.

We searched for HBV associated factors in children through univariate analyses (Chi-square or Fisher's exact test) and a multivariate analysis (backward logistic regression). All variables of which "p" was under 0.30 in univariate analysis were included in initial model of multivariate analysis. Alpha threshold was 5% for bilateral formulation.

3. RESULTS

HVB infection screening among the family circle of the 44 studied index subjects was about 39 spouses and 96 children. Index subjects' median age was 43.1 ± 7.49 years ranging from 28 to 58. Average number of children per subject index was 2.3 ± 1.1 ranging from 1 to 5 children. HIV test was negative in all their parents. Characteristics of index subjects and their children at inclusion are summed up in **Tables 1** and **2**.

The 96 children's median age was 9.3 ± 4.55 years ranging from 1 to 15 years. HBV infection in children was 24% (HBcAb were presents in 23 out of 96). HBsAg was present in only 4 of these 23 children (17.4%), that is an overall prevalence of 4.2% (4 children out of 96). Three of these 4 HBsAg-positive children had not received any Hepatitis B vaccine (one aged 14 years old and two aged 15 years old). The 4th one aged 2 years old was immunized within the framework of the enlarged vaccination program (3 doses at the 6th, 10th and 14th week after birth). Vaccination coverage was 44.8% (43 children out of 96). These vaccination coverage among children above 12 years was significantly less than that of those aged 12 or less (1 of 37 children >12 years, that is 2.7% versus 42 of 59 children ≤12 years, that is 71.2%; $p < 0.001$). None of the 96 children had drug addiction history or risk sexual behavior. Relationship between HBV serological status of children and baseline characteristics of index subjects and their children is summed up in **Table 3**.

Table 1. Baseline characteristics of 44 index subjects.

Baseline characteristics of 44 index subjects		
Median age, years (IQR*)	42	38 - 47
Female gender, *n* (%)	20/44	(45.5)
Positive HBe antigen (Ag), *n* (%)	11/44	(25)
Positive anti-HBe antibodies (Ab), *n* (%)	33/44	(75)
HBV DNA ≥ 2000 IU/ml, *n* (%)	18/44	(40.9)
Serum transaminase level (ALT*) > UNV*, *n* (%)	14/44	(31.8)
Spouse at home, *n* (%)	39/44	(88.6)
HBV complete vaccination of spouses, *n* (%)	05/39	(12.8)
HBV serological status of spouses:		
Positive HBsAg and positive HBcAb, *n* (%)	06/39	(15.4)
Positive HBcAb without HBsAg, *n* (%)	17/39	(43.6)
Negative HBsAg and negative HBcAb, *n* (%)	16/39	(41)
Median number of children (IQR)	2	(1 - 3)

*IQR = Interquartile range; HBV DNA = Hepatitis B virus DNA; ALT = Alanine aminotransferase (UNV: 50 UI/mL); UNV = Upper normal value.

Table 2. Baseline characteristics of 96 children.

Baseline characteristics of 96 children		
Median age, years (IQR*)	9	(5 - 14)
Female gender, *n* (%)	52/96	(54.2)
HBV vaccination coverage of children, *n* (%)	43/96	(44.8)
HBV serological status of children:		
Positive HBsAg and positive HBcAb, *n* (%)	04/96	(4.2)
Positive HBcAb without HBsAg, *n* (%)	19/96	(19.8)
Negative HBsAg and negative HBcAb, *n* (%)	73/96	(76)

*IQR = Interquartile range.

4. DISCUSSION

In HBV high-endemic areas, like Côte d'Ivoire, the two main transmission ways are perinatally or vertical transmission and intrafamilial horizontal transmission in early

Table 3. Relationship between HBV serological status of children and baseline characteristics of index subjects and their children.

Baseline characteristics	Univariate analyses			**Multivariate analysis**	
	HBV serological status of children				
	Infected	Uninfected	p	HR (95% CI)	p
	n (%)	*n* (%)			
Children >12 years	16/23 (69.6)	21/73 (28.8)	<0.001		
Male gender children	10/23 (43.5)	34/73 (46.6)	0.795		
Unvaccined children	22/23 (95.7)	31/73 (42.5)	<0.001	30.9 (3.8 - 95.2)	0.003
Index subjects >42 years*	17/23 (73.9)	30/73 (41.1)	0.006		
Female gender index subjects	5/23 (21.7)	36/73 (49.3)	0.02		
Both parents' infected*	22/23 (95.7)	34/65 (52.3)	<0.001	7.9 (1.9 - 60.2)	0.03
Vaccined spouses*	1/23 (4.4)	8/65 (12.3)	0.436		
Biological results of index subjects					
ALT* > UNV*	14/23 (60.9)	21/73 (28.8)	0.005		
Positive HBeAg	14/23 (60.9)	9/73 (12.3)	<0.001		
HBV DNA* ≥2000 IU/ml	17/23 (73.9)	21/73 (28.8)	<0.001	11.5 (2.7 - 25.2)	0.001

*Median age of index subjects, results for 88 children of 39 index subjects living with a regular spouse; ALT = Alanine aminotransferase (UNV: 50 UI/mL); UNV = Upper normal value; HBV DNA = Hepatitis B virus DNA.

childhood [5,7]. From teenage, there exist other HBV transmission additional risks, especially sexual transmission during unprotected intercourse and drug addiction [5,7]. We excluded from our study all parents whose children were above 15 years old to limit weight of all these additional factors.

Most of index subjects were married and had at least two children. HBV infection prevalence in children of index subjects in our study was 24%. That just shows the importance of HBV infection systematic screening of the HBsAg-positive subjects' family circle.

Out of 96 children of index subjects, only 43 were immunized (44.8%). This weak immunization coverage was above all observed before HBV vaccine integration of into the EVP in 2000. Indeed, rate of immunized children aged above 12 years was 2.7% and that of the children aged 12 years or less was 71.2% ($p < 0.001$). Among the 43 immunized children, only one aged 2 years had been screened HBsAg positive. The latter must have been infected during perinatal period, before administration of the 1st HBV vaccine dose of the 6th week. HBV vaccine must therefore be privileged in delivery room to be more efficient (immunization at birth and particularly during the 12 first hours). Indeed, in two observational cross-sectional studies made in sub-Saharan Africa, HBV infection vertical transmission rate in newborns of HBsAg mothers was 32.8% [8] and 37.1% [9]. Transmission rate was significantively associated with HBeAg mother status. When HBeAg was present in the mother, infected newborns rate was respectively 66.7% [8] and 54.5% [9] whereas it was respectively 26.9% [8] et 29.2% [9] when HBeAg was absent in mother. In addition, in children who escaped form vertical transmission, there exist a risk of horizontal intrafamilial transmission before immunoprophylaxis through vaccination; that risk of horizontal intrafamilial transmission is favored by promiscuity and share of objects between parents and children or between children themselves [10].

Three independent factors were significantively associated with HBV in children of index subjects: a HBV viremia higher than 2000 IU/ml in index subjects, existence of HBV infection in two parents and absence of HBV vaccine for children. Many works have showed that the key risk factor for HBV infection vertical transmission was viremia in mother within perinatal period [11-15]. Viremia in parents is as well an important risk factor for horizontal intrafamilial transmission of HBV infection [16], especially in children who escaped from vertical transmission and who did not receive HBV vaccine. Owing to promiscuity, intrafamilial transmission risk for the infection is all the more important since both parents are infected. Even though it is not always easy in studies to put things in perspective between vertical transmission and horizontal intrafamilial transmission, there seems the existence of a significative association between female index subjects and HBV high prevalence in these parents' children [17-19]. Of these three risk factors identified in our study, the most easily controlla-

ble is HBV vaccine. Current vaccinal strategy must be modified on the one hand starting immunization from birth in all children whatever HBV status the mother has, on the other hand, prescribing a nucleosidic analogs from the 28th week to HBsAg-positive mothers who have strong HBV viremia. So, even if children are systematically immunized at birth, searching for HBsAg in pregnant women must be made compulsory and quantify HBV load in HBsAg-positive pregnant women in order to identify those to whom a treatment through nucleosidic analogs will be proposed for maximal reduction of HBV infection perinatal transmission. Acquired immunization through vaccination will allow to later preventing children from other HBV transmission risks, especially horizontal intrafamilial transmission.

5. CONCLUSION

Immunization coverage for children of our index subjects was insufficient, especially before introduction of HBV vaccine into the EVP. Outside vertical transmission, those children were more exposed to HBV intrafamilial transmission when they were not immunized against HBV, when both parents were infected and when HBV viremia of index subjects was higher than 2000 IU/ml. Immunization coverage must therefore be improved, immunization must be started at birth and nucleosidic analogs must be proposed to HBsAg-positive pregnant women with strong viremia.

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