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HEPATITIS B ELIMINATION IN CHILDREN OF SLOVENIAN ORIGIN BORN IN SLOVENIA AFTER THE INTRODUCTION OF PREVENTIVE STRATEGIES: THE RESULTS OF A NATIONAL STUDY

ELIMINACIJA HEPATITISA B PRI OTROCIH SLOVENSKEGA IZVORA, ROJENIH V SLOVENIJI, PO UVEDBI PREVENTIVNIH UKREPOV: REZULTATI NACIONALNE RAZISKAVE

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ABSTRACT

Introduction: In Slovenia national strategies to prevent hepatitis B virus (HBV) infection in children were introduced in the mid-nineties. The aim of the present study was to analyze the epidemiological characteristics of chronic hepatitis B infection in children in Slovenia after the introduction of mandatory HBV vaccination of children and mandatory screening of pregnant women for HBV surface antigen (HBsAg) with consecutive active and passive immunization of newborns of HBsAg-positive mothers.

Methods: Children from all regions of Slovenia whose blood samples tested positive for HBsAg at the national reference laboratory for viral hepatitis between January 1997 and December 2010 were included. Demographic, epidemiological and virological data were reviewed retrospectively. Statistical evaluation of the patients' characteristics was performed and possible trends during the observation period determined.

Results: Among 52 HBsAg-positive children, there were 22 (42.3%) girls and 30 (57.7%) boys. Among 40 children tested for HBeAg, 17 were positive (42.5%). The most frequent risk factor for acquiring HBV infection was "presence of HBV infection within the family" (24/35; 68.8%). A significant association between the presence of HBeAg and a viral load of >20,000 IU/ml was found (p=0.001). The difference in the proportion of children of Slovenian origin born before 1994 and after was statistically significant (p=0.039). A statistically significant negative linear trend of the number of diagnosed children in the observed period was found (p=0.006).

Conclusions: Prevention strategies adopted in the mid-nineties have resulted in the elimination of chronic hepatitis B in children of Slovenian origin born in Slovenia.

Keywords:
chronic hepatitis B, prevention strategies, vaccination, mandatory screening, HBsAg, pregnant women

IZVLEČEK

Uvod: *V Sloveniji je bila sredi devetdesetih let prejšnjega stoletja uvedena nacionalna strategija za preprečevanje okužbe z virusom hepatitisa B (HBV) pri otrocih. Cilj naše raziskave je bil analizirati epidemiološke značilnosti kronične okužbe otrok s HBV v Sloveniji po uvedbi obveznega cepljenja otrok proti HBV in obveznega presejanja nosečnic na površinski antigen HBV (HBsAg) s posledično aktivno in pasivno imunizacijo novorojenčkov HBsAg pozitivnih mater.*

Metode: *Vključeni so bili otroci iz vseh regij Slovenije, katerih vzorci krvi so bili pozitivni na HBsAg v nacionalnem referenčnem laboratoriju za virusni hepatitis med januarjem 1997 in decembrom 2010. Demografski, epidemiološki in virološki podatki so bili pregledani retrospektivno. Opravljena je bila statistična ocena značilnosti pacientov in ugotovljeni možni trendi v obdobju opazovanja.*

Rezultati: *Med 52 otroki, pozitivnimi na HBsAg, je bilo 22 (42,3 %) deklet in 30 (57,7 %) dečkov, njihova povprečna starost (± standardni odklon - SD) je bila 13,3 (± 5,5) let. Med 40 otroki, testiranimi na HBeAg, je bilo 17 pozitivnih (42,5 %). Najpogostejši dejavnik tveganja za pridobitev okužbe s HBV je bil "okužba s HBV v družini" (24/35; 68,8 %). Ugotovljena je bila tudi pomembna povezava med prisotnostjo HBeAg in virusnim bremenom > 20.000 IU/ml (p = 0,001). Razlika v deležu otrok slovenskega izvora, rojenih pred letom 1994 in po njem, je bila statistično značilna (p = 0,039). Ugotovljen je bil statistično značilni negativni linearni trend števila otrok, okuženih s HBV v opazovanem obdobju (p = 0,006).*

Zaključki: *Preventivne strategije, sprejete sredi devetdesetih let, so privedle do eliminacije kroničnega hepatitisa B pri otrocih slovenskega izvora, rojenih v Sloveniji.*

Ključne besede:
kronični hepatitis B, preventivni ukrepi, cepljenje, obvezno testiranje, nosečnice

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1 INTRODUCTION

With an estimated 257 million chronically infected persons worldwide, hepatitis B virus (HBV) infection still represents a major global public health problem, despite the long-term existence of highly effective hepatitis B prevention strategies, including the HBV vaccine (1-3). In Europe the average HBV prevalence has been estimated at 2%, whereas in highly endemic areas of Africa and the Pacific it is up to 22.7% (4). In Slovenia, HBV prevalence has been estimated at below 1% (5).

In 2016, the World Health Organization (WHO) adopted a strategy to eliminate HBV infection by 2030 and stated five core interventions: three doses of hepatitis B vaccination for children, a hepatitis B birth-dose to prevent perinatal transmission, blood and injection safety, harm reduction (syringe/needle set for people who inject drugs) and testing services/treatment (1, 6-9). Since perinatal or early postnatal transmission represents the most significant source of chronic HBV infection (CHB) globally, in 2017 WHO recommended that all infants should receive their first dose of hepatitis B vaccine as soon as possible after birth (10). According to the WHO report, up until 2016 active immunization against hepatitis B had been included in the national programs of mandatory vaccination of children in 98% of member states (11). In 2015, global coverage with the three doses of hepatitis B vaccine in infancy reached 84%, while coverage with the initial birth dose was reported still to be low at 39% (1). In 2016 in the United States of America only 60.6% of newborns received the HBV vaccine (12).

In Slovenia, preventive vaccination against hepatitis B was included in the national program of mandatory vaccination of children in December 1997; children born after 1992 were vaccinated at the age of six, before entering elementary school, and from 2020 children are vaccinated against HBV at the age of 3 months (13).

Additionally, all the newborns of HBV surface antigen (HBsAg)-positive mothers receive specific human immune-globulins immediately after birth together with the first dose of HBV vaccine (14).

Mandatory screening of pregnant women for HBsAg was introduced in Slovenia in 1994 (15). According to the latest European Centre for Disease Prevention and Control (ECDC) data, antenatal screening for hepatitis B has been implemented in 23 out of 26 European countries; in the majority of reporting countries (8/13), screening coverage was ≥95% (16).

The aim of the present study was to analyze epidemiological characteristics of CHB in children in Slovenia after the introduction of mandatory HBV vaccination and mandatory screening of pregnant women for HBsAg with consecutive active and passive immunization of newborns of HBsAg-positive mothers.

2 METHODS

2.1 Patients

All HBsAg-positive children 18 years of age or younger extracted from the central database totaling 1,729 persons from all regions of Slovenia who tested positive for HBsAg at the national reference laboratory for viral hepatitis (Laboratory for Molecular Microbiology and Diagnostics of Hepatitis and HIV/AIDS, Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana) between January 1997 and December 2010 were included in this study.

Available epidemiological and clinical characteristics were reviewed from the medical documentation at five hospitals responsible for the management of patients with viral hepatitis (University Medical Centers Ljubljana and Maribor, and General Hospitals in Celje, Novo Mesto, and Murska Sobota).

Origin was defined as “country, race, or social class of a person’s parents or ancestors” (17).

2.2 Serological and molecular methods

In all samples HBsAg and HBeAg were determined using the ARCHITECT Immunoassay analyzer (Abbott, Weisbaden, Germany) and HBV DNA viral load using the real-time polymerase chain reaction (RT-PCR) based Abbott RealTime HBV Test (Abbott). Viral load was categorized according to the clinical implications into three ranges: ≤ 2,000 IU/mL, 2,000-20,000 IU/mL and ≥ 20,000 IU/mL (18).

2.3 Statistical methods

Associations were tested using univariate and multiple logistic regression, likelihood ratio or the Mann-Whitney U test, as appropriate. Possible time trends during the observation period were determined. No correction for multiple comparisons was made. Significance tests were two-sided. P-values ≤0.05 were considered statistically significant. Statistical analysis was performed using R program 3.1.1 and SPSS 23.0.

3 RESULTS

A total of 52 eligible children were included. Table 1 shows the baseline characteristics of the included children.

A statistically significant association between the presence of HBeAg and a viral load above 20,000 IU/ml (p=0.001) was found. Table 2 presents the demographic, epidemiological, clinical and virological characteristics of the included children regarding presence/absence of HBeAg.

Table 1. Demographic, epidemiological, clinical and virological characteristics of included children (N=52).

	%
Gender (N=52)	
Female	22 (42.3)
Male	30 (57.7)
Mean age (SD; range) (years) (N=52)	13.3 (5.5; 0-18)
Risk factors (N=35)	
Unknown	8 (22.9)
Presence of HBV infection within the family	24 (68.8)
Blood/blood products transfusion	1 (2.9)
High-risk sexual behavior	1 (2.9)
Surgical procedure in the past	1 (2.9)
ALT (N=29) (μkat/L)	
≤ 0.56	14 (48.3)
> 0.56	15 (51.7)
HBeAg (N=40)	
Negative	23 (57.5)
Positive	17 (42.5)
Viral load (IU/ml) (N=24)	
< 2,000	9 (37.5)
2,000-20,000	0 (0)
> 20,000	15 (62.5)

HBV – hepatitis B virus, ALT – alanine aminotransferase, SD – standard deviation, IU – international units

Out of the 52 children, 47 were of Slovenian origin. The oldest child of Slovenian origin included in the study was born in 1979. Altogether 41/52 (78.8%) children were born before or in 1994, 39 of Slovenian origin and two of foreign parents. There were 11/52 (21.1%) children born after 1994, eight Slovenians and three foreigners. The difference in the proportion of children of Slovenian origin born before 1994 and after 1994 was statistically significant (p=0.039). Children of Slovenian origin born after 1994 with CHB were born in 1996, 1998, 2003, and the last chronically infected child in 2004 (Table 3). Unfortunately, we found clinical data for three children only who are still followed. Two of them have active CHB and one seroconverted. Interestingly, the last chronically infected child was born to a father who acquired HBV infection while vaccinated in the Yugoslav National Army (YNA) (19).

Table 2. Demographic, epidemiological, clinical and virological characteristics of included children regarding presence/absence of hepatitis B virus e antigen (N=40).

Domain	HBeAg-negative n (%)	HBeAg-negative n (%)	p - value
Gender (N=40)	23 (57.5)	17 (42.5)	
Female	9 (39.1)	8 (47.1)	0.616[a]
Male	14 (60.9)	9 (52.9)	
Median age (range) (years) (N=40)	14 (0-18)	17 (0-18)	0.334[c]
Risk factors (N=28)	17 (60.7)	11 (39.3)	
Unknown	4 (23.5)	3 (27.3)	0.824[b]
Presence of HBV infection within the family	12 (70.6)	6 (54.5)	0.389[b]
Blood/blood products transfusion	1 (5.9)	0 (0)	0.312[b]
High-risk sexual behavior	0 (0)	1 (9.1)	0.165[b]
Surgical procedure in the past	0 (0)	1 (9.1)	0.165[b]
ALT (μkat/L)(N=22)			
≤ 0.56	10 (66.7)	2 (28.6)	
> 0.56	5 (33.3)	5 (71.4)	0.092[b]
Viral load (IU/ml) (N=20)			
< 2,000	8 (66.7)	0 (0)	0.001[b]
2,000-20,000	0 (0)	0 (0)	
> 20,000	4 (33.3)	8 (100)	

a=hi-square test; b=likelihood ratio test; c=Mann-Whitney U test

HBV – hepatitis B virus, ALT – alanine aminotransferase, HBeAg – hepatitis B virus e antigen, IU – international units

Table 3. Number of children of Slovenian origin by year of birth (N=47).

YEAR OF BIRTH	NUMBER OF CHILDREN
1979	1
1980	2
1981	3
1982	4
1983	5
1984	3
1985	3
1986	2
1987	4
1988	2
1989	2
1990	6
1991	0
1992	0
1993	0
1994	2
1995	0
1996	5
1997	0
1998	1
1999	0
2000	0
2001	0
2002	0
2003	1
2004	1
2005	0
2006	0
2007	0
2008	0
2009	0
2010	0
Sum	47

A statistically significant negative linear trend (p=0.019) was present in the annual number of diagnosed children in the period 1997–2010, as shown in Figure 1, while in the same period there was no linear trend present in the entire population (p=0.978) (Figure 2).

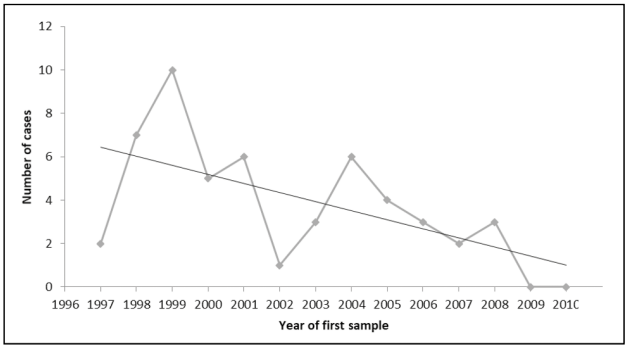

Figure 1. The annual number of newly registered hepatitis B virus chronically infected children in the studied period 1997–2010 (N=52).

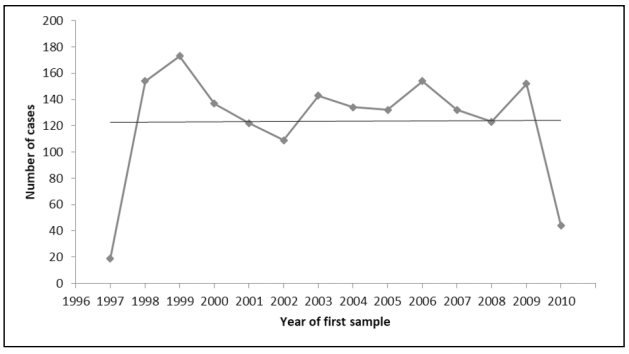

Figure 2. The annual number of newly registered hepatitis B virus chronically infected persons in the studied period 1997–2010 (N=1.729).

4 DISCUSSION

To the best of our knowledge this is the first study describing the epidemiological characteristics of children chronically infected with HBV in Slovenia. The most common risk factor among children included in our study was “presence of HBV infection within the family” (68.8%), as has been reported in other European countries (20). In countries with low HBV prevalence the most common routes of childhood infection are perinatal transmission or transmission in early childhood (10). Consequently, antenatal screening, antiviral prophylaxis in pregnancy and early HBV vaccination are vital for preventing HBV infection (21, 22).

Our results have shown that mandatory vaccination of children and screening of pregnant women for HBsAg with consecutive immunization of newborns of HBsAg positive mothers significantly reduced the incidence of CHB among children born in Slovenia. To the best of our knowledge, currently there are only four children with CHB in follow-up at the main Slovenian hospital, University Medical Center Ljubljana (UMCL), none of them having been born in Slovenia (they were born in China, Ghana, Ukraine and Thailand, respectively) (Breda Zakotnik, MD, B.Sc, personal communication, unpublished data).

Similar reports on the effectiveness of the HBV child vaccination come from Bulgaria (23), Taiwan (24) and China (25). There are also reports on protection from HBsAg carriage after hepatitis B immunization in the general population (26).

An HBV DNA viral load greater than 20,000 IU/ml was found in a significant proportion of HBeAg-positive children. This finding is consistent with the natural course of HBV infection in the Mediterranean region (27, 28). Our children and young adults are still in phase two of the natural course of the disease (HBeAg-positive chronic hepatitis) (18), for which a high HBV DNA viral load is characteristic.

The main strength of our study is its national coverage, while a major limitation is that some statistical analysis had to be performed in smaller subgroups due to lack of data. There is also a potential chance that some children and pregnant women were never diagnosed at the national reference laboratory for viral hepatitis, but at Blood Transfusion Centers of Slovenia. In further research, which is currently in progress, we will focus on a determination of the prevalence of HBsAg-positive pregnant women in Slovenia in the past 20 years and try to obtain data on chemoprophylaxis of pregnant women and the proportion of newborns of HBsAg-positive mothers who received passive and active immunization, with the aim of updating national guidelines for the treatment of HBsAg-positive pregnant women and their newborns.

5 CONCLUSIONS

Our study showed that prevention strategies adopted in the mid-nineties – mandatory vaccination of children against hepatitis B and mandatory HBsAg screening of pregnant women – have resulted in complete elimination of CHB in children of Slovenian origin born in Slovenia after 2004. We sincerely hope that elimination of CHB in children in Slovenia will soon be followed by the same achievement in other countries in the region, or at least that we can show the way forward to achieving this goal.

CONFLICT OF INTEREST

The authors declare that no conflicts of interest exist.

FUNDING

None.

ETHICAL APPROVAL

The study was approved by the National Medical Ethics Committee of the Republic of Slovenia on May 4th, 2015 (consent number: 6/04/15).

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