CHRONIC HEPATITIS B INFECTION IN PEDIATRIC POPULATION: A RETROSPECTIVE STUDY FROM A TERTIARY CENTER IN NORTH-EASTERN ROMANIA

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CHRONIC HEPATITIS B INFECTION IN PEDIATRIC POPULATION: A RETROSPECTIVE STUDY FROM A TERTIARY CENTER IN NORTH-EASTERN ROMANIA (Abstract): Chronic viral hepatitis B is the precursor stage of cirrhosis and the 10th leading cause of death worldwide. WHO estimated in 2019 that approximately 296 million people were chronically infected with the hepatitis B virus and over 800,000 deaths. **The aim of study** was to describe characteristics of chronic HBV infection in pediatric population from a tertiary center in North-Eastern Romania. **Materials and Methods**: A retrospective study was conducted on 148 pediatric patients with chronic HBV infection who had visits from 2011 to 2019 to St. Mary's Hospital Iasi (Romania). The HVB infection in study group was analyzed regarding demographic characteristics, distribution of pediatric patients in relation to vaccination status, risk factors, HBV infection stage, and clinical manifestations. The qualitative variables were characterized through frequencies distributions. The quantitative variables were characterized through descriptive statistics (averages, standard deviations). $P < 0.05$ was the threshold for significance. **Results**: Most of the patients (87,83%) had vertical transmission, while 18.91% had horizontal transmission. Most of the pediatric population was vaccinated (87.83%), while 11.48% had incomplete vaccination. The most common risk factor was vertical transmission (81.8%), followed by horizontal transmission, surgical interventions (10.13%), frequent hospitalizations (4.1%), and dental procedures (3.4%). Among patients with HBV infection, most of them presented loss of appetite (16.2%), followed by abdominal pain (12.8%), hepatomegaly (12.2%), and physical asthenia (4.1%). **Conclusions**: Most children from our study were in chronic hepatitis B phase and immune-tolerant phase. Pediatric patients with chronic viral B infection can experience a slow progression of the disease without specific signs and symptoms for a long period, especially when the diagnosis is made at an infant or young child age. **Keywords**: CHILDREN, HEPATITIS B VIRUS, VACCINATION, TRANSMISSION.

Hepatitis B represents a significant health challenge worldwide, characterized by high rates of morbidity and death. Annually, 1.5 million new cases of HBV infection emerge, despite the effectiveness of vaccination and the potential to curb viral replication and spread through medication (1). It is estimated that the global preva-

lence of HBV infection in children up to 5 years of age is 1.3%, significantly lower compared to the 1980-2000 period (4.7%) (2). However, despite increased access to immunization, about 2 million new HBV infections are recorded each year in the 0-5 years age group (3). Given that the majority of HBV infections occur through vertical transmission from mother to child during pregnancy or childbirth, there is an increased risk (over 90%) of chronic HBV infection (over 6 months). HBV infection can progress to hepatic fibrosis, cirrhosis, and hepatocellular carcinoma, although pediatric patients are rarely diagnosed with these conditions (4). However, approximately 3-5% of children with chronic HBV infection develop cirrhosis, while 0.01-0.03% develop hepatocellular carcinoma (5). In the initial stage of HBV infection, typically contracted at birth, the virus shows high replication levels. This is characterized by the presence of HBeAg and extremely high HBV DNA concentrations in the blood, often exceeding 100 million or even 1 billion IU/mL. This stage, known as the HBV infection HBeAg positive (immune-tolerance phase), usually persists for a period ranging from 10 to 30 years. During this time, the likelihood of naturally eliminating HBeAg from the body is quite low. Statistically, after two decades of being infected, the cumulative probability of spontaneously losing HBeAg is about 2% in the first three years, increasing to only 15% after 20 years (6). The second phase of HBV infection, hepatitis B HBeAg positive (often referred to as the immune-clearance or immune-active phase), typically emerges in the third or fourth decade of the disease in individuals who contracted HBV early in life. This phase is marked by the continued presence of serum HBeAg, a gradual reduction in HBV DNA levels, and either increased or variable ALT levels, indicative of HBeAg positive chronic hepatitis. Some patients may undergo multiple exacerbations characterized by temporary loss of HBeAg and periodic elimination of HBV DNA from the blood. In such cases, the recurring episodes of hepatitis increase the likelihood of developing cirrhosis and hepatocellular carcinoma. HBeAg negative hepatitis is identified by the absence of HBeAg in the serum, often accompanied by the presence of anti-HBe antibodies. This condition also features ongoing or variable serum HBV DNA levels that are generally lower than those found in HBeAg positive patients, along with fluctuating or consistently high ALT levels (7). HBeAg negative hepatitis is identified by the absence of HBeAg in the serum, often accompanied by the presence of anti-HBe antibodies. This condition also features ongoing or variable serum HBV DNA levels that are generally lower than those found in HBeAg positive patients, along with fluctuating or consistently high ALT levels (7). HBeAg negative chronic HBV infection, also known as inactive hepatitis phase, is characterized by the presence of antibodies against HBeAg, HBV DNA levels that are undetectable or low (below 2000 IU/mL), and normal ALT levels as defined by standard cutoff values (the upper limit of normal [ULN] is approximately 40 IU/L). Despite having normal serum ALT levels, patients with HBeAg negative chronic infection may still experience histologic inflammation and/or fibrosis (8).

AIM of study was to describe characteristics of chronic HBV infection in pediatric population from a tertiary center in North-Eastern Romania.

MATERIALS AND METHODS

A retrospective study was conducted on 148 pediatric patients with chronic HBV

infection, with at least one medical visit to St. Mary's Hospital Iasi (Romania), from January 1, 2011 to December 31, 2019.

Chronic HBV infection was defined as the presence of hepatitis B surface antigen (HBsAg) for at least 6 months.

The inclusion criteria were:

- age from 0 to 18 years at their initial pediatric visits with the diagnosis of chronic HBV infection;

-the presence of hepatitis B surface antigen (HBsAg) for at least 6 months.

Each patient's demographic characteristics, clinical history, family history of immediate family members, prior HBV vaccination, and laboratory values were extracted from patient charts. Characteristics of HBV vertical transmission were as follows: mother' age and occupation, comorbidities, maternal HBeAg status, type of delivery. Patient charts were reviewed for HBV vaccination and receipt of hepatitis B immunoglobulin (HBIG). The phases of chronic HBV infection were analyzed cross-sectionally according to the following laboratory values: HBeAg status, anti-HBe status, ALT, and HBV DNA levels. The characteristic was based on the American Association for the Study of Liver Diseases (AASLD) hepatitis B guidance 2018 (9). The HVB infection in study group was analyzed regarding demographic characteristics, distribution of pediatric patients in relation to vaccination status, risk factors, HVB infection stage, and clinical manifestations

Statistical analysis. The statistical analyses were performed in SPSS 29.0. The qualitative variables were characterized through frequencies distributions. The quantitative variables were characterized through descriptive statistics (averages, standard deviations). $P < 0.05$ was the threshold for significance.

RESULTS

Table I exposes demographic characteristics of the study population. On age groups, the distribution was as follows: 0-1 yrs. (20.27%), 2-5 yrs. (25.35%), 6-10 yrs. (22.97%), 11-14 yrs. (18.91%), 15-18 yrs. (11.48%). Regarding gender, 52.02% were boys and 47.97% were girls. Regarding the birth type, 80,4% were born naturally and 19.59% were born through C-section with overall median weight at birth 3,200 g. Most of the patients (81.08%) had vertical transmission, while 18.91% had horizontal transmission. Most of the pediatric population was vaccinated (87.83%), while 11,48% had incomplete vaccination. Most of the patients (72.29%) were breastfed, while 27.7% were bottle-fed. Patients from low socioeconomic families (rural provenience) (61.48%) predominated over patients from urban families (38.51%).

Distribution of pediatric patients in relation to vaccination status and birth weight is exposed in figure 1 (93.2% were children with $\geq$ 2,500 g, 4.7% were between 1,500-2,500 g, and 2.0% were < 1,500g) (fig. 1).

According to the study data, 3 children weighed < 2,000 g and 7 children between 1500 and 2,000 g. Among those with LBW (Low Birth Weight), only one was born to a mother with HBV infection, and 2 of them did not have a complete vaccination schedule, meaning they were either not vaccinated by the time of discharge from the maternity hospital or at the age of one month. For those born weighing less than 2,500 g, all were vaccinated. The viral status of the mothers at the time of birth is unknown (tab. II).

The distribution of patients from HBsAg positive mothers. The frequency of administering hepatitis B immunoglobulin to children from HBsAg positive mothers is presented in Fig. 2 (3.4% - received hepatitis B immunoglobulin; 35.1% - did not

receive; 61.5% - unspecified).

The distribution of patients according to risk factors is presented in Table II. It is noted that the most common risk factor is vertical transmission (81.8%), followed by horizontal transmission, surgical interventions (10.13%), frequent hospitalizations (4.1%), and dental procedures (3.4%).

TABLE I.

Demographic characteristics of the pediatric population

Characteristics		Patients (148)
Age (years)	0-1 2-5 6-10 11-14 15-18	30 (20.27%) 39 (25.35%) 34 (22.97%) 28 (18.91%) 17 (11.48%)
Gender	M F	77 (52.02%) 71 (47.97%)
Birth	Natural C-section	119 (80.40%) 29 (19.59%)
Transmission	Vertical Horizontal	121 (81.08%) 27 (18.91%)
Vaccination	Yes No Incomplete	130 (87.83%) 1 (0.67%) 17 (11.48%)
Alimentation in the 1st year of life	Breastfed Bottle-fed	107 (72.29) 41 (27.70%)
Provenience	Urban Rural	57 (38.51%) 91 (61.48%)

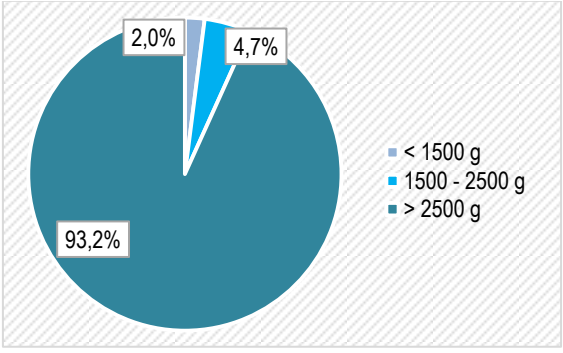

Fig.1. Distribution of pediatric patients in relation to vaccination status and birth weight

TABLE II.

Vaccination status related to birth weight

		Birth weight						Total	
		< 1,500 g		1,500 – 2,500 g		➢ 2,500 g			
		N	%	N	%	N	%	N	%
		Pearson Chi square = 9.333 / p = .053							
Vaccinated	Yes	1	33.3%	6	85.7%	123	89.1%	130	87,8%
	Incomplete	2	66.7%	1	14.3%	14	10.1%	17	11,5%
	No	0	0.0%	0	0.0%	1	0.7%	1	0,7%
Total		3	100,0%	7	100.0%	138	100.0%	148	100.0%

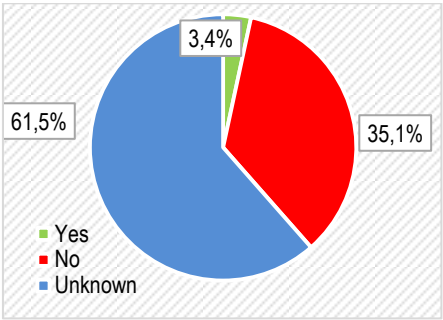

Fig. 2. Ig antihepatitis B administration to children from Ag HBs positive mothers

TABLE III.

Risk factors in HBV infection

	n	%
Tonsillectomy	4	2,7
Tonsillectomy	2	1,4
Dental procedures	5	3,4
Appendectomy	2	1,4
Fractures	2	1,4
Frequent hospitalizations	6	4,1
Frenectomy	1	,7
Other surgical interventions	2	1,4
Laceration on ring finger	1	,7
Polypectomy	1	,7
Intrafamilial transmission	3	2,0
Vertical transmission	121	81,8
Horizontal transmission	27	18,2
Blood transfusions	1	,7
Total	148	100,0

Among the patients, all phases of HBV infection were detected, with the majority (49.3%) being diagnosed in the phase of chronic viral hepatitis B Ag HBe +, followed by HBV infection Ag HBe + in 27.7% of children. Generally, the second phase, that of immunotolerance, predominates in the pediatric age, but in our group, the majority had hepatocytolysis syndrome over x2 VN (normal value) (fig. 3).

Out of a total of 148 children, 19.6% presented with anti-HBe antibodies at the time of diagnosis. Spontaneous seroconversion was predominantly recorded in those with chronic HBeAg- infection (73.9%), and 81.8% of those with chronic HBeAg- hepatitis were positive for anti-HBe antibodies. It is known that seroconversion in the HBe system is more common in the pediatric population than in adults (tab. IV).

The clinical manifestations recorded in the pediatric population with HBV infection are presented in Table V. Among patients with HBV infection, most of them presented loss of appetite (16.2%), followed by abdominal pain (12.8%), hepatomegaly (12.2%), and physical asthenia (4.1%). Other nonspecific signs were rec-

orded such as arthralgia (2%), headache (2%), dysphagia (1.4%), or weight stagnation (1.4%). Other possible clinical manifestations were also sub febrility, sleep disturbances, or scleral and skin sub icterus.

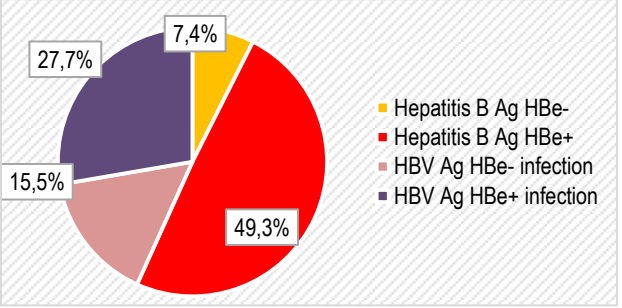

Fig. 3. Distribution of pediatric population related to stage of HVB infection

TABLE IV.

Distribution of pediatric patients related to Ac anti HBe to diagnostic time

		HBV infection stage to la DG								Total	
		VHB Ag HBe+ infection		VHB Ag HBe- infection		VHB Ag HBe+ hepatitis		VHB Ag HBe- hepatitis			
		N	%	N	%	N	%	N	%	N	%
		Pearson Chi-square = 91.130 / p <.001**									
Anti HBe Ab at diagnostic time	negative	39	95.1%	6	26.1%	72	98.6%	2	18.2%	119	80,4%
	positive	2	4.9%	17	73.9%	1	1.4%	9	81.8%	29	19,6%
Total		41	100.0%	23	100.0%	73	100.0%	11	100.0%	148	100.0%

TABLE V.

Clinical manifestation in pediatric population with HBV infection

	n	%
Nausea/vomiting	6	4.1
Loss of appetite	24	16.2
Physical asthenia	6	4.1
Semi-formed stools	6	4.1
Abdominal pain:	19	12.8
- diffuse abdominal pain	11	7.4
- right hypochondrium pain	7	4.7
- epigastric pain	1	.7
Hepatomegaly	18	12.2
Odynophagia	8	5.4
Cough	10	6.8
Rhinorrhea / pharyngeal congestion:	10	6.8
- pharyngeal congestion	3	2.0
- nasal obstruction	2	1.4
- rhinorrhea	5	3.4

	n	%
Nosebleed	6	4.1
Fever	7	4.7
Fatigability	5	3.4
Other:	26	17.6
psychomotor agitation	1	.7
arthralgia	3	2.0
headache	3	2.0
lipothymic states	1	.7
constipation	1	.7
dysphagia	2	1.4
dysphonia	1	.7
overweight	1	.7
jaundice	1	.7
menometrorrhagia	1	.7
menorrhagia	1	.7
metrorrhagia	1	.7
pallor	1	.7
paresthesia of extremities	1	.7
rectal bleeding	2	1.4
weight stagnation	2	1,4
scleral icterus	1	,7
scleral-cutaneous icterus	1	,7
cutaneous icterus, sallow facies	1	,7

DISCUSSION

Although there are many studies that have investigated the risk factors for HBV infection in infants, data from Romania is very scarce and an urgent update is requested. In our country, the major route of HBV infection in children is the vertical transmission which despite universal immune prophylaxis, remains evident and is associated with maternal HBV DNA levels (10). Most children from our study were in chronic hepatitis B phase and immune-tolerant phase, 37.8% were without clinical manifestations, while 36.48% did not have liver enzymes increased.

The immunization schedule is dependent on the birth weight and the infectious status of the mother. All newborns weighing 2,000 grams or more from HBsAg-negative mothers are given the vaccine within the first 24 hours, while those weighing less than 2,000 grams can be vaccinated upon discharge or at the age of one month. If the mothers are HBsAg positive at birth, then the vaccine and HBIG are administered within the first 12 hours, regardless of the newborn's birth weight. If the immunological status of the mother is unknown, the vaccine is administered within the first 12 hours after birth to all newborns (11, 12). The fact that 11.48% patients were incomplete vaccinated and 1 didn't get any vaccines shows that there is a lack in family education regarding the immunization scheme especially since most of them (64.70%) are from urban area. Regarding the HBIG administration, unfortunately is not available in maternities and all the mothers must buy it at a quite high price, even if is indicated to all newborns to HBsAg positive mothers. So, a priority in providing immunoglobulin to children from positive mothers by the government is mandatory. Another aspect is the temporary absence of anti-hepatitis B vaccine in ma-

ternities, and some parents forget or delay the time of vaccination. Until 6 weeks of life is used only the monovalent vaccine. After this age is used the polyvalent vaccine in three doses, first at 6 weeks, the next two at 1 month between them. Also, vaccination is safe and indicated in pregnant women or other high-risk groups (13). Besides that, the evaluation of infants should be done at 9-15 months of life, to be sure that they developed an immune response. Usually those who didn't get antibodies are with low weight birth or other risk factors as chronic diseases, genetic factors, HIV coinfection.

It is already known that the most effective way to prevent vertical transmission of the hepatitis B virus is through the administration of the vaccine and hepatitis B immunoglobulin at birth, reducing the risk from 5-25% to 0.7-1.1% (14). However, the risk is particularly present if the mother was not monitored during pregnancy and did not receive the necessary treatment. In our group, only 5 patients received HBIG in the first hours after birth (5.4%), 52 did not receive it (35.1%), while for the remaining 61.5%, relatives stated they were unaware of this immunization or whether the newborn was immunized (15). The low percentage of HBIG administration indicates a lack of information among pregnant women, a deficient interdisciplinary relationship between the family doctor, obstetrician, neonatologist, and gastroenterologist, and the absence of a national program to ensure the availability of immunoglobulin in maternity wards. We observed a downward trend in those with chronic hepatitis Ag HBe+ in relation to age, with the most diagnoses being in infants and young children, then after the age of 2 years, the number of diagnosed cases gradually decreases until 18 years of age.

We found that most of risk factors, besides vertical transmission, are represented by surgical interventions. It is known that until now, the main mode of hepatitis B virus transmission was through infected blood via inadequately sterilized medical instruments (injections, manicure, cosmetic procedures, tattoos, intravenous drugs, piercing), but today there are disposable needles, blood screening for transfusion, and accessible protective equipment (16). In 3 of the patients, we noted familial transmission, knowing the father's positive history and the mother's negative for HBV infection. This can occur either using personal items (razor blades, toothbrushes, scissors, tweezers, sewing needles, glucose meters) or through close interpersonal contact (scratches, domestic accidents with cuts). Therefore, it is requested education of all family members about periodic HBV testing to identify and promptly treat any new cases, education on hygiene and preventive measures to reduce the risk of transmission and avoiding direct contact with the blood or open wounds of infected individuals without adequate protection measures.

It is known that most children are asymptomatic (17). Indeed, in our study, among those with HBeAg+ infection, 56.1% did not show specific signs and symptoms, the results are roughly the same for those with HBeAg- infection, and among those with chronic HBeAg+ hepatitis, 75.3% presented clinical symptoms and signs such as diffuse abdominal pain, in the right hypochondrium or epigastrium, nausea, vomiting, loss of appetite, and physical asthenia.

CONCLUSIONS

Most children from our study were in chronic hepatitis B HBeAg+ phase and chronic HBeAg+ infection phase (immunotolerant). Pediatric patients with chronic viral B infection can experience a slow

progression of the disease without specific signs and symptoms for a long period, especially when the diagnosis is made at an infant or young child age.

CONFLICT OF INTEREST AND FUNDING

The authors declare that there is no conflict of interest and they received no funding.

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