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Hepatitis B Virus Infection in a Group of Iraqi Children in Baghdad

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Original Article

Abstract

Background: *HBV infection is a problem of public health, and a major cause of mortality and morbidity in our country since it lies within the areas of intermediate to high (2-7%) carrier rate.*

Objective: *To study certain demographic factors of the patients affected by the HBV, the possible sources of infection, the behavior of the disease and the response to the available treatment.*

Patients and Methods: *This was a cross-sectional study carried out in Baghdad city, the capital of Iraqi, during a period of 11 months investiating 110 child patients who were testing positive for HBs Ag and attending our hospital. Data were collected using a pre-constructed data collection sheet which used to gather data regarding the following; child's age, sex, residence, medical history, surgical history, blood transfusion history, vaccination status and family history. A thorough clinical examination was performed for all patients by specialist pediatricians. Laboratory and other necessary investigations were performed accordingly.*

Results: *Findings showed that most of the patients were older than 5 yrs. (80.7%). Males constituted (61.81%). Most patients came from Baghdad and Anbar being (42.73%) and (32.73%), respectively. Horizontal transmission was responsible for 76.37% of the cases. Most patients (87.24%) were asymptomatic and having high viral loads (74.44%). Unvaccinated patients constituted (47.27%) of the sample and (72.22%) of them had viral loads >100000 copies/ml. HBV and HCV coinfection was present in (12.73%) of the patients. SVR with undetected viral DNA was achieved in (18.18%) of the cases whom they completed 52 wks. of INF therapy, and (10%) of the cases completed 52 wks. of lamivudine therapy. HBeAg seroconversion was achieved in (18.18%) of the cases whom they completed 52 wks. of INF therapy and (11.11%) of the cases whom they completed 52 wks. course of combined INF and lamivudine. Cirrhosis was found in (4.55%) of the cases.*

Conclusion: *Blood born infection and vertical transmission were common routes of transmission in our pediatric society and treatment response was close to the international figures.*

Keywords: *Hepatitis B Virus Infection, Epidemiology, Transmission, Children.*

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1. INTRODUCTION

Hepatitis B is one of the most common viral infections worldwide. Hundreds millions of individuals are chronic carriers and mainly responsible for the spread of the disease. There has been a safe and effective vaccine against hepatitis B virus (HBV) since the early 1980s and in 1992 the WHO recommended integrating the vaccine into immunization programs, which has led to a reduction in the burden of the disease, in the percentage of carriers and morbidity and mortality. However, factors such as vertical transmission, immigration and adoption maintain the circulation of the hepatitis B virus in the pediatric setting (1). Hepatitis B (HBV) is not uncommon among children. Neonatal hepatitis or congenital hepatitis is a term used to indicate hepatitis that accompany the child from birth. Babies born to mothers with hepatitis are at risk of contracting hepatitis. In most cases, this happens when the mother is unaware of her hepatitis disease and the baby is delivered by cesarean section. So that doing testing for hepatitis before pregnancy and during pregnancy is very important and can help the doctors on how the mother should give birth (2,3).

Hepatitis B virus belongs to the Hepadnaviridae family. It is a small DNA virus exhibits distinctive characteristics similar to retroviruses. It replicates via an RNA intermediate and has the capability to integrate into the genome of the host organism. The distinctive characteristics of the HBV replication cycle confer upon a specific capacity to persist within the infected cells. Virological and serological assays have been developed to facilitate the detection of different manifestations of HBV-associated illness and to aid in the management of chronic hepatitis B infection. The infection caused by the hepatitis B virus (HBV) results in a diverse range of liver diseases, such as acute conditions (invoving fulminant hepatic failure), as well as chronic hepatitis, cirrhosis, and hepatocellular cancer (4).

Eight genotypes of HBV have been described, and its mechanism of action and liver damage is given by two mechanisms, cytopathic and immune-mediated. Viral clearance is associated with a specific polyclonal response of TCD4 and TCD8 cells to the epitopes of all HBV proteins (5). Transmission of HBV can be vertical or horizontal; vertical transmission is through the placenta during pregnancy, at the time of delivery or in the postnatal period (intimate contact with maternal secretions) (6). The most frequent form of transmission is that which occurs during childbirth. Horizontal transmission occurs by intimate contact with the carrier; sexual, parenteral

route and secretions. Despite vaccination and gamma globulin, the risk of vertical transmission varies depending on the maternal viral load: Mother in immunoactive phase (positive HBsAg and HBeAg and high viral load): 1-5%. Chronic carrier mother (positive HBsAg and anti-HBe Ab with low viral load): < 1%. Perinatal infection in 90% of cases become chronic. In children contracted infection at their one to five years of age, 20-50% became. Conversely, only 5% of HBV infection became chronic among adults (6). Children at high risk of HBV infection include those who are born to mothers with hepatitis B, children who need frequent blood transfusion, who underwent surgical procedures and those with renal failure and managed by dialysis (7). Acute HBV infection characterized by the presence of hepatitis B surface antigen (HBsAg) in the blood. This antigen usually becomes positive between weeks one and ten after contact (in transplacental transmission it can be positive at birth while in transmission during childbirth it will be positive after a few weeks of life). The clinical characteristics of acute infection is divided into three phases; after an incubation period of 14 to 180 days, initial pre-icteric or Prodromal phase characterized by flu-like symptoms or digestive symptoms and sometimes Characteristic rashes called Gianotti-Crosti. Icteric phase where a progressive decrease in prodromal symptoms (although asthenia usually persists) and presence of dark color urine, yellow eyes, and light colored stool, in this phase prodromal symptoms improved and it is last from few days to < 6 weeks. The convalescence phase where there is a gradual improvement and recovery. The interpretation of serological tests results varies according to the age of child and the antibody or antigen that found in the sera of the child. Chronic infection It is defined by the persistence of HBsAg in serum for six months or more. There are four successive and well-differentiated phases: Immune tolerance phase, Immune active phase, Immune control phase and Immune clearance (cure) phase. In children who are infected through perinatal transmission the sequence of these phases is typically seen (8–10). Clinical manifestations are varied according to the disease status; Most children with hepatitis B do not have specific symptoms, but the most common symptoms of hepatitis B in children are: vomiting, fatigue, fever, decreased appetite, yellow skin and sclera. The acute hepatitis B is characterized by: fatigue, reduced appetite, nausea, vomiting, abdominal pain, pain in the right hypochondrium, subfebrile body temperature, jaundice, dark urine, light-colored stools, arthralgia and headache(8–10).

Prodromal phase characterized by flu-like symptoms or digestive symptoms and sometimes characteristic rashes called Gianotti-Crosti (11)

Chronic HBV characterized by: mostly asymptomatic course or fatigue, emotional lability, feeling of discomfort in the right hypochondrium, epistaxis, possible arthralgias. Fatigue, jaundice, nausea, telangiectasias (stellar hemangiomas), edema, ascites, peripheral edema, sleep disturbances, gastrointestinal bleeding may be noted in patients with a severe course or in patients with liver cirrhosis(12). Extra-hepatic manifestations such as nodular periarteritis, nephropathy and cryoglobulinemia (13)

Diagnosis of HBV in children based on the physical examination that may shows hepato- and splenomegaly, telangiectasia, palmar erythema, ascites, and other signs. Diagnostic measures are aimed at establishing and confirming the diagnosis of HBV, differential diagnosis of it with other diseases and assessment of the risk of severe complications. Diagnostic approaches include blood tests; serological tests, liver enzymes, liver function, complete blood cell count (CBC). Coagulation tests, antibodies polymerase chain reaction. Imaging are also required to confirm the diagnosis and monitor the sequel of the disease. X- Ray, sonography, computed tomography (CT) scan, Magnetic resonance imaging can show detailed images and very effective in liver examination and make the diagnosis easier and earlier. In some cases liver biopsy may performed. The possible complications of hepatitis in children include liver failure, hepatic cancers and death, The ultimate goal of treatment is to prevent progression to cirrhosis and hepatocellular carcinoma and is achieved through seroconversion of HBeAg to HBeAc, serum clearance of HBV DNA and normalization of ALT, as well as abscence of HBsAg (cure) (14–17).

Although hepatitis B vaccine has reduced HBV carriers worldwide. Managing persistent HBV infection in children is still a challenge. The main goal of antiviral therapy in pediatric hepatitis B patients is HBeAg seroconversion, which reduces HBV replication. Children with prolonged HBV infection may spontaneously seroconverted to HBeAg. When decompensated cirrhosis is absent, interferon-alpha is the first antiviral drug. Lamivudine, adefovir, entecavir, and tenofovir are nucleos(t)ide analogues (NUCs) all are available for pediatric patients, however age restrictions regarding the use of these therapies are differ. Nucleoside analogues (NAs) are the preferred antiviral treatment for decompensated cirrhosis. However, the optimal duration of

treatment and the potential side effects of some medications in children are still unclear. From other point of view, the therapeutic effects and the clinical impact of antiviral medications in pediatric HBV patients still need further clarification (18–20). Hence we aimed to study certain demographic factors of the patients affected by the HBV, the possible sources of infection, the behavior of the disease and the response to the available treatment.

2. PATIENTS and METHODS

This was a cross-sectional study carried out in Baghdad city, the capital of Iraqi, during a period of 11 months investiating 110 child patients who were testing positive for HBs Ag and attending our hospital. Data were collected using a pre-constructed data collection sheet which used to gather data regarding the demographic characteristics of the patients and the clinical findings laboratory findings and other investigations including the following:

• Chil's age at diagnosis ,
• Chil's sex,
• Residency,
• History of acute hepatitis /jaundice,
• Medical history,
• Surgical history,
• History of blood transfusion,
• Vaccination status,
• Family history of hepatitis B.,
• Clinical findings on examination,
• Labarotary findings and other investigations

Study Protocol and Method:

- A thorugh physical examination was done for all patients by specialist pediatricians (the Researchers) looking for signs of acute hepatitis or those of chronic liver disease.
- In all patients, laboratory investigations were performed accordingly including complete blood count (CBC), liver function tests, PCR assessment for the viral load (which was available for 90 patients), and lately it was possible to study the antibody profile of the

virus done at the Central Health Laboratory. Other laboratory investigations were performed when required.

- Ultrasound/Doppler examination was done for the assessment of liver texture, ascites & state of portal circulation,
- Follow up: Sixty one Patients had normal transaminases and were assigned as immunotolerant & kept on every 3 month follow up of liver function & other features of inflammation with annual follow up of PCR viral load assessment.
- Detecting signs of active hepatitis was taken as an indication of treatment, Interferon 3megaunit/m2 surface area or pegylated interferon PEGASYS 100microgram/m2 surface area.
- Those with increased transaminases were considered to be immunoreactive and given treatment, they were 49 patients.
- PCR was repeated 3 months after treatment to document responsiveness, another reading at the end of INF therapy (one year), if undetected virus another reading done 6 months after completing therapy to document either sustained viral response or relapse.
- Response to treatment was considered by seroconversion of HBeAg positive to positive antibody to HBeAg and negative HBeAg.(69). Resistance is defined by increased viral load during treatment. (failed to reduce viral load by >102 after 3 mos. starting therapy). Patients unresponsive to INF were shifted to Lamivudine 3 mg/kg; some were already on Lamivudine during their cytotoxic therapy.Some patients who were resistant or intolerant to therapy, who were older than 15yrs & could manage the drug were put on entecavir.
- Liver cirrhosis was considered when an abdominal ultrasound showing fibrosis.

Statistical analysis:

Data were analyzed with the aid of statistical package for social sciences (SPSS) version 24, Microsoft Excel program and Epicalc-2000 software ®. Descriptive statistics and cross tabulation were performed according to the type of variables.

3. RESULTS

The demographic characteristics of the studied group are shown in (**Table 1**). It had been found that 80% of the 110 patients aged 5 years or older. Males contributted for 61.8%. Large proportion of patients were resident of Baghdad, (42.7%), followed by Anbar (32.7%), all other provinces contributted for 24.5%. Vertical transmission reported in a total of 24 patients (21.8%) of them 59.1% aged below 5 years, 19.6% aged 5-10 years and only 4.8% aged > 10 years. Malignacy reported in 41 patients; 38/41 had blood transfusion and the remaining 3 had not. Most malignat cases were aged 5 years and older. Surgery, family contact, and others were reported in 6.4%, 14.5% and 1.8%, respectively. Unknown mode of transmission or source of infection reported in 20 /110 patients (18.2%). All these findings are shown in (**Table 2**). Only 5 (12.7%) of cases had history of jaundice/acute hepatitis. Viral load (PCR) was available for 90 of the total 110 patients. Most patients had high viral load category (>100000 copies/ml), (**Table 3**). Regarding the vaccination status , 48 patients were vaccinated and 62 were unvaccinated. Viral load (PCR) was available for only 20 /48 vaccinated and 52/62 unvaccinated patients. Most of the unvaccinated patients had high viral load range, (**Table 4**). We found 14 combined HBV and HCV infection of them 11 (78.6%) had high viral load of > 100000 copies/ml, (**Figure 1**). Regarding the treatment, 30 patients received INF, 10 patients received Lamivudine and 9 patients received combination of both treatments. Among the 30 patients who received INF treatment, 11 completed the 1 yr. course of therapy. 2 patients showed SVR and another 2 have been seroconverted (positive antibody to HBeAg and negative HBeAg). However, more detailed outcomes of treatment are summarized in (**Table 5**)

Table 1. Demographic characteristics of the studied group (N=110)

Variable		**No.**	**%**
Age (year)	<5	22	20.0
	5 - 10.	46	41.8
	>10	42	38.2
Sex	Male	68	61.8
	Female	42	38.2
Residence	Baghdad	47	42.7
	Al-Anbar	36	32.7
	Other provinces	27	24.5

Table 2. Distribution of mode of transmission according to child's Age

Mode of Transmission		Age (year)						Total	
		<5		5 - 10		>10			
		No.	%	No.	%	No.	%	No.	%
Vertical		13	59.1	9	19.6	2	4.8	24	21.8
Horizontal									
Malignancy	Had blood transfusion	2	9.1	13	28.3	23	54.8	38	34.5
	No blood transfusion	0	0.0	2	4.3	1	2.4	3	2.7
Surgery		2	9.1	2	4.3	3	7.1	7	6.4
Family contact		1	4.5	9	19.6	6	14.3	16	14.5
Others		0	0.0	0	0.0	2	4.8	2	1.8
Unknown		4	18.2	11	23.9	5	11.9	20	18.2
Total		**22**	**100.0**	**46**	**41.8**	**42**	**100.0**	**110**	**100.0**

Table 3. Distribution of history of Jaundice/acute hepatitis and viral load according to child's Age.

Variable		<5 yrs.		5-10 yrs.		>10 yrs.		Total	
		No.	%	No.	%	No.	%	No.	%
History of Jaundice/acute hepatitis	Yes	5	4.5	4	3.6	5	4.5	14	12.7
	No	17	15.5	42	38.2	37	33.6	96	87.3
	Total	**22**	**20.0**	**46**	**41.8**	**42**	**38.2**	**110**	**100.0**
Viral Load (copies/ml) (N=90)	<10000	3	3.3	4	4.4	7	7.8	14	15.6
	10000-100000	1	1.1	2	2.2	6	6.7	9	10.0
	>100000	15	16.7	30	33.3	22	24.4	67	74.4
	Total	**19**	**21.1**	**36**	**40.0**	**35**	**38.9**	**90**	**100.0**

Table 4. Distribution of viral load according to the status of vaccination of studied group

Status of vaccination	Viral Load (copies/ml)						Total	
	<10000		10000-100000		>100000			
	No.	%	No.	%	No.	%	No.	%
Primary	3	4.2	1	1.4	4	5.6	8	11.1
Delayed Vaccination	1	1.4	1	1.4	8	11.1	10	13.9
Primary and Booster	0	0.0	1	1.4	1	1.4	2	2.8
Unvaccinated	9	12.5	3	4.2	40	55.6	52	72.2
Total	13	18.1	6	8.3	53	73.6	72	100.0

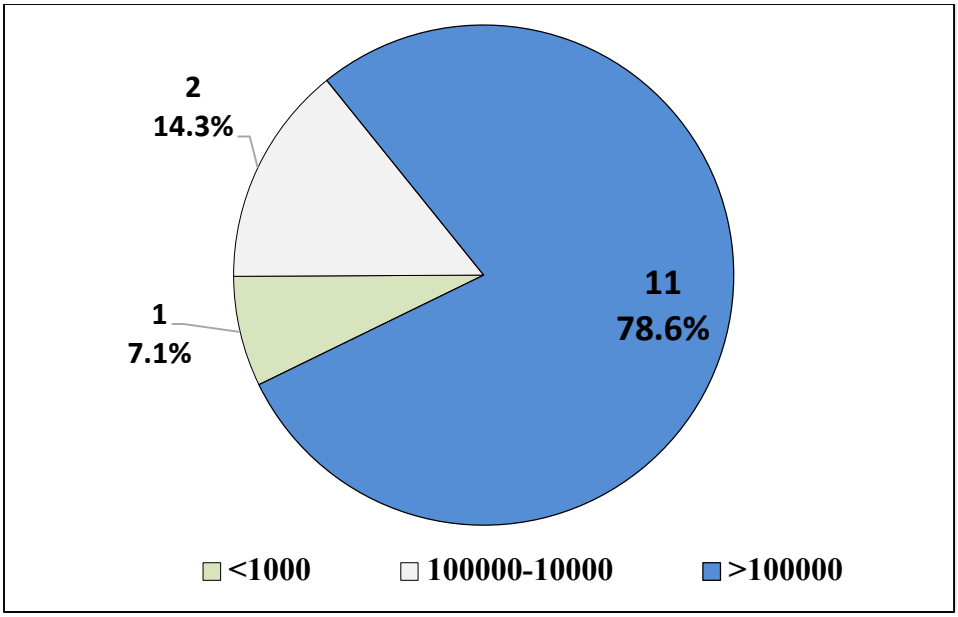

Figure 1. Distribution of the reported 14 Combined Hepatitis B and C infection according to viral load (copies/ml)

Table 5. Response to the type of therapy received by children

Variable	INF (n=30)		Lamivudine (n=10)		Combined INF & Lamivudine (n=9)	
	No.	%	No.	%	No.	%
Responsive	6	20.0	2	20.0	2	22.2
SVR	2	6.7	1	10.0	7	77.8
Relapse	0	0.0	1	10.0	-	-
Resistant	6	20.0	3	30.0	-	-
Non Adherent	8	26.7	3	30.0	4	44.4
Non Compliance	4	13.3	-	-	3	33.3
BM Suppression	4	13.3	-	-	1	11.1

BM: Bone Marrow

4. DISCUSSION

Hepatitis B virus infection is a signifciant public health problem worldwide represents a major cause of mortality and morbidity, particularly in developing countries. Most countries in the Middle East region including Iraq are still considered at intermediate to high carrier rate of (2-7%) (21,22). In our studied group, males were dominant and contributted for 61.81%, this finding agreed that reported by Zubair et al. (23) who found 54% males and 46% females among HBV cases. Also Nwokediuko found higher rate of 79.2% in males (24). In Turkey, Dikici et al. found no difference between both genders (25). However, the studied Iraqi sample, represented cases referred to tertiary care center, most of them had been treated for other illnesses that put them at risk of acquiring the infection, so it doesn't represent the actual prevalence in the community. Among our cohort. (21.8%) acquired the infection vertically which is less than the rate reported by El-Raziky from Egypt (26) where vertical transmission reported in 50% of cases and concluded that vertical transmission is an important risk factor for acquisition of HBV among children born after the era of mass vaccination in Egypt. Worldwide; the risk of perinatal infection is 5–20% in infants born to HBsAg-positive mothers and 70–90% if the mother is HBeAg positive In Asia and most of Africa, chronic HBV infection is common and usually acquired perinatally or in childhood (27). High risk of infection reported in infants born to mothers who are positive for both HBsAg and HBeAg (2,3). HBeAg status for the mother was

not available in our study and the Egyptian study and could be responsible for the discrepancies. An increased prevalence among children older than 5 years implying the big role of horizontal transmission in acquiring the infection added to that is the increased number of malignancy cases in this age group which affect humoral response to hepatitis B vaccination (28). Regarding the residence of cases, most came from Baghdad and Al-Anbar, this was not unexpected becaue the location of our hospital , however, about quarter of cases came from other provinces due to more facilities in our hospital. An earlier Iraqi study put Baghdad in the 1 – 1.99% region and Anbar in the 2-2.99% region were as Al-Qādisiyya, Maysn, Wāsit and Dhī Qār in addition to Kurdistan governorates were areas of lowest endemicity in Iraq with a prevalence of 0-0.99% (29). Nearly 75% of the studied sample had high viral loads which expected since viral loads tend to be very high in children (30). In our study, only 48 patients were vaccinated and greatly increasing the risk of acquiring infection in endemic country (31). Most of our malignancy patients in the study (38/41) had multiple transfusions of blood/blood product adding to the risk of malignancy for acquiring the disease as documented in a Pakistani study (32). In our study, 14 patients (12.7%) had co-infection with hepatitis C virus which is comparable to previous studies (33). Treatment with INF was started as a monotherapy for 30 of our studied sample, of those 11 finished one year treatment course and achieved an SVR in 2 patients and another 2 responded by serocoversion to HBeAg negative. These results were approximate to the results obtained in earlier clinical trials(34). A different results was obtained in Italy where much less than what we obtained regarding seroconversion (35). The discrepancies in the results of the different studies might be due, in part, to the different therapeutic regimens and varying populations of patients included in these trials. A certain number of factors are predictive of poor response to IFN; one of them is infection with HBV at birth or early in life . Relapse by detecting the viral DNA 6 months after stopping INF monotherapy was not noticed in our study which could be attributed to the shorter time of our study. However, an earlier study involving large cohort of patients treated with INF and had been followed for an average of 4 years after treatment revealed a sustained virologic response (defined as 20,000 copies/mL of serum HBV DNA at the 6-month post-treatment interval) occurred in 43% of patients . However, this response was durable in only 25% up to slightly more than half of the initial responders at the 4-year interval (36). A Chinese study published confirmed chronic hepatitis B patients including 403 HBeAg-positive and 120

HBeAg-negative patients, who were treated with INF for 6-25 months and had been followed up every 3-6 months after stopping treatment (37). Adherence to INF therapy had some limitations in our study including frequent interruptions because of unavailability of the drug, noncompliance of the patient/family and development of side effects of which bone marrow depression involving leukopenia, thrombocytopenia or both which was noticed. These results are comparable to that obtained by other researchers while disagreed others (37–39) The discrepancies can be attributed to the differences in the sample sizes. Lamivudine monotherapy was well tolerated by our study sample with one limitation which is frequent unavailability of the drug. Our patients responded by decreased viral load in (20%) of patients after 3 months of treatment, and (10%) of patient has undetected viral DNA over the last 3 years. One (10%) patient had relapsed. These results differ from studies published regarding lamivudine monotherapy (40,41) . However, the trial of these treatment is out of the scope of our study and it needs to be investigated in separated clinical trials for longer time

However, we observed that combined INF and lamivudine in the regimen used is not superior to monotherapy, which is comparable to other studies (42)

5. CONCLUSIONS

Hepatitis B is a prevalent problem in our pediatric society with preponderance of male. Most cases were residents in Baghdad and got their infection via male preponderance. Vertical transmission was the main cause of infection in children less than 5 years while transverse transmission was the commonest in older children. A high rate of unvaccinated children was noticed. Blood born infection was the probable source of transmission in high proportion of patients. Hepatitis B and C coinfection was prevalent in the studied group. Response rate to the available drugs for the pediatric cases was somewhat near to the international figures, with >60% of the pediatric cases being unresponsive. Cirrhosis was found in 4.55% of the studied cases. Therefore we recommend enhancement of universal vaccination dealing with mothers as possible carriers, if their serological status is unknown. Screening of all pregnant women, vaccination of previously unvaccinated children, adolescents and adults and also we recommend the strict application of all preventive measures

Ethical Clearance:

Ethical issues were taken from the research ethics committee. Informed consent was obtained from parents or care-giver of all participated children. Data collection was in accordance with the World Medical Association (WMA) declaration of Helsinki for the Ethical Principles for Medical Research Involving Human Subjects, 2013 and all information and privacy of participants were kept confidentially.

Conflict of interest: Authors declared none

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