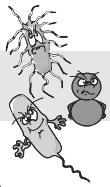

Chronic Hepatitis B Virus in Children in Israel: Clinical and Epidemiological Characteristics and Response to Interferon Therapy

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Key words: hepatitis B virus, transaminase levels, transmission, side effects

Abstract

Objective: To describe the clinical and epidemiological features of hepatitis B virus infection in Israeli children, and to evaluate their response and compliance to therapy.

Methods: We retrospectively studied 51 patients (34 males, 17 females), aged 2–18 years, from several medical centers in Israel.

Results: Of the 51 patients, 38 with elevated transaminase, positive hepatitis B e antigen and/or HBV DNA, and histologic evidence of liver inflammation were treated. Interferon was administered by subcutaneous injections three times a week for 3–12 months (dosage range 3–6 MU/m^2). Only 16% were native Israelis, while 78% of the children were of USSR origin. A family history of HBV infection was recorded in 25 of the 51 patients (9 mothers, 16 fathers or siblings). Five children had a history of blood transfusion. The histological findings were normal in 3 patients, 24 had chronic persistent hepatitis, 14 had chronic active hepatitis and 2 had chronic lobular hepatitis. Five children also had anti-hepatitis D virus antibodies. Twelve of the 38 treated patients (31.5%) responded to IFN completely, with normalization of the transaminase levels and disappearance of HBeAg and HBV DNA. In no patient was there a loss of hepatitis B surface antigen. The main side effects of IFN were fever in 20 children, weakness in 10, headaches in 9, and anorexia in 6; nausea, abdominal pain, and leukopenia were present in 3 cases each. The response rate was not affected by age, country of origin, alanine/aspartate aminotransferase levels, or histological findings. However, a history of blood transfusion was a predictor of good response, 60% vs 27% ($P<0.05$).

Conclusions: We found IFN to be a safe and adequate mode of treatment in children with chronic HBV infection, regardless of their liver histology and transaminase levels. Therefore, in view of the transient side effects associated with this drug, we recommend considering its use in all children with chronic hepatitis B.

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Hepatitis B is a significant cause of chronic liver disease in most parts of the world. It is estimated that more than 300 million adults and children worldwide are chronically infected with HBV [1]. The majority of infected individuals are asymptomatic, but the disease is associated with a high morbidity rate due to complications such as progression to cirrhosis and hepatocellular carcinoma, which can eventually lead to death.

In the pediatric population infected during infancy, the rate of progression to chronicity following infection with HBV is significantly higher than in adults [2]. Therefore, early diagnosis of HBV hepatitis is imperative in order to initiate treatment of the infected children.

The efficacy and safety of interferon treatment in HBV-infected adults is well established [3–5]. For children, the current data are relatively limited, although several studies have shown benefits of this drug in the pediatric population. The reported response rate is variable, ranging from 0% to 40% among studies from different parts of the world [6–14]. In Israel, the prevalence of chronic hepatitis B in the pediatric population has increased considerably during the last decade due to the large wave of immigration from endemic countries, such as the former USSR and Ethiopia. The effect of IFN on children, and especially in Israel with its distinct population characteristics, has not been studied in depth. We retrospectively investigated pediatric patients with HBV infection who were being seen in several medical centers in Israel, and describe

HBV = hepatitis B virus
IFN = interferon
HBeAg = hepatitis B e antigen

here the epidemiological features of this population, the course of the disease, and the response to IFN therapy.

Patients and Methods

Our study included 51 children (34 boys, 17 girls) who had been diagnosed as having chronic hepatitis B between 1990 and 1997 in five medical centers in Israel. The diagnosis was based on positive HBsAg and/or HBeAg, abnormal liver function tests, and signs of chronic inflammation on liver biopsy. We studied the patients retrospectively, retrieving data from their medical records and from interviews with the patients or their parents.

Thirty-eight children were treated with recombinant-α-interferon (Roferon-A; Hoffman-LaRoche, Switzerland, or Intron-A, Schering, USA). The indications for treatment were increased levels of serum ALT/AST, positive serologic tests (including HBsAg, HBeAg, and HBV DNA), and signs of chronic inflammation on liver biopsy. Thirteen patients who were not treated had either transaminase levels within the normal range, or normal to near-normal liver histology.

Markers of HBV infection (HBsAg, anti-HBs antibodies, HBeAg, anti-Hbe antibodies) were tested with Microparticle Enzyme Immuno Assay (AXSYN, Abbott), and anti-HDV antibodies with Enzyme Immuno Assay (QUANTUM, Abbott). Liver function tests were performed by the Hitachi analyzer 747 (Japan), according to the Scandinavian method. Serum HBV DNA was measured with a standard dot blot hybridization technique. Liver biopsies were performed percutaneously using the Jamashidi needle.

Interferon was administered by subcutaneous injections, and the dosage ranged from 3 to 6 MU/m^2 3 times a week (3 MU/m^2 in 45% of the children, and 5–6 MU/m^2 in 55%), and treatment duration was 3–12 months. The median follow-up was 24 months (range 4–78). The follow-up consisted of repeated routine blood tests (complete blood count, SMAC, ALT/AST) and serological and virological tests.

Statistical analysis

The Chi-square test was used to compare characteristics of responders with those of non-responders. The variables analyzed were age, gender, place of birth, ALT levels at diagnosis, histological findings at diagnosis, and source of infection. Fisher's exact test was used to compare the rate of infection by blood transfusion between responders and non-responders. The paired sample *t*-test was performed in order to compare pretreatment and post-treatment transaminase levels.

Results

The characteristics of patients included in the study group are listed in Table I. The median age was 10 years (range 2–18). Forty patients (78%) were born in the former Soviet Union, and only 8 children (16%) were native Israelis. The other three children were immigrants from Ethiopia and Romania.

Table I. Demographic characteristics of the patients (n=51), and transmission routes

Male/Female	34/17 (67%, 33%)
Median age (yr, range)	10 (2–18)
Origin	
Former USSR	40 (78%)
Israel	8 (16%)
Ethiopia	2 (4%)
Romania	1 (2%)
Transmission	
Vertical	9 (18%)
Horizontal	16 (31%)
Blood transfusion	5 (10%)
Unknown	21 (41%)

Table 2. Presenting symptoms, laboratory and histological findings

None	29 (57%)
Abdominal pain	14 (27%)
Headache	2 (4%)
Nausea, vomiting	2 (4%)
Anorexia	2 (4%)
Weakness, fatigue	1 (2%)
Irritability	1 (2%)
Abnormal ALT	40 (78%)
ALT≥1.5 times the normal value*	27 (53%)
ALT≥4 times the normal value*	13 (25%)
HBsAg positive	51 (100%)
HBeAg positive	40 (78%)
HBV DNA positive	30 (58%)
Anti-HDV positive	5 (10%)
Histology**	
CPH	24 (47%)
CLH	2 (4%)
CAH	14 (27%)
Cirrhosis	1 (2%)
Normal liver	3 (6%)

* Normal values up to 40 U/L
** Liver biopsy was performed in 44/51 patients
CPH = chronic persistent hepatitis, CLH = chronic lobular hepatitis, CAH = chronic active hepatitis.

The transaminase values were increased in 40 patients. The average pretreatment ALT value was 123.9±80 U/L (mean±SD). Serological tests showed that all the children were positive for HBsAg, 40 patients had HBeAg, and 5 patients also had antibodies to HDV. HBV DNA was found in the serum of 30 patients [Table 2] .

Liver biopsy was performed in 44 patients, revealing chronic persistent hepatitis in 24 (54%), chronic lobular hepatitis in 2, chronic active hepatitis in 14 (32%), cirrhosis in one, and normal histology in 3 [Table 2].

The mode of transmission, as judged by the patient's and family history, was vertical (perinatally) in 9 children, horizontal (intrafamilial) in 16, by blood transfusion in 5, and unknown in 21 [Table I].

Most of the children were asymptomatic throughout the course of their illness. There was no presenting symptom in 57%, who were diagnosed because of increased transaminase levels revealed in routine blood tests or following the diagnosis of hepatitis B in another member of the family. In symptomatic children, the most common

ALT/AST = alanine/aspartate transaminase

the family. In symptomatic children, the most common presenting symptom was abdominal pain, recorded in 14 patients (27%). Less common symptoms were headache, nausea, anorexia, fatigue and irritability [Table 2].

Thirty-eight patients were treated with interferon-α. Twelve children (31.5%) responded to IFN therapy by clearance of HBeAg, seroconversion to anti-HBeAg, decrease of HBV DNA to undetectable levels, and normalization of the transaminase values. One of the complete responders was HbeAg negative before treatment (mutant type), and one was HBV DNA negative. All these 12 children had a prolonged response that lasted at least 6 months. Four of them responded during the course of IFN treatment, while the other eight showed response between 2 and 18 months after termination of IFN treatment. One patient had a partial response that lasted less than 6 months. Twenty-five children (66%) failed to respond. Clearance of HBsAg did not occur in any of the patients during follow-up [Table 3].

The treatment was well tolerated by the children. Almost all of them received injections from the medical staff members, usually the nurses. One child was injected by his mother, and one teenager injected herself. Compliance was generally good. Only two children discontinued treatment against medical advice. The main side effects of IFN were fever (40%), weakness and fatigue (20%), headache (18%), anorexia (12%), nausea and vomiting (6%), abdominal pain (6%), leukopenia (6%), anemia (4%) and urticaria (2%). Eight patients did not have any side effects, whereas in two patients the side effects (urticaria in one and dyspnea in the other) were so severe that IFN treatment was discontinued

Age, gender, liver histology and ALT level at diagnosis did not affect the response rate. The route of transmission, on the other hand, did have a statistically significant influence on response: children who acquired HBV through infected blood transfusion had a higher response rate than other children, 3/5 vs. 9/38 ($P=0.04$). In addition, children who were born in the USSR tended to respond at higher rates, but this tendency was not statistically significant. Five of our chronic hepatitis B patients also demonstrated anti-HDV antibodies in their serum. Four of them were given IFN but none showed any response to therapy. Thirteen children were not treated with IFN; they could not be used as a control group because they were not randomized. There were significant differences in disease characteristics between the treated and non-treated groups, mainly in the transaminase values that were within the normal range in the latter. Two children from the non-treated group showed spontaneous remission after 4 months and 42 months, respectively.

Table 3. Response to interferon therapy

Response	At 3 months	At end of treatment	At end of follow-up
Complete response			12 (31.5%)
LFT normalization	1	5	17
Loss of HBsAg	0	0	0
Loss of HBeAg	2	4	11*
Loss of HBV DNA	2	5	11**
No response			25 (66%)
Transient response			1 (2.5%)

* One of the 12 complete responders was HbeAg negative before treatment (mutant type).

** In 1 of the 12 responders HBV DNA was not detected before treatment.

Discussion

The study population had unique demographic characteristics. Eighty percent of the children were new immigrants born in Eastern Europe, mainly in countries of the former Soviet Union, and only 16% were born in Israel. Since 1992, HBV vaccine has been routinely administrated to all newborns born in Israel, whereas no routine vaccination against HBV is given in the former USSR. Therefore, the prevalence of chronic hepatitis B in the Israeli population has been increasing since the large wave of immigration from those highly endemic regions began, and the prevalence of HBV hepatitis among these new immigrants is high [15,16].

We found a relatively high rate of vertical and horizontal transmission (18% and 31%, respectively). Infection due to contact with contaminated blood and blood products was less common (10%). This is consistent with the fact that most of the children came from highly endemic countries where vertical and horizontal transmission is the major route of virus acquisition [17,18]. In 19 children (37%), the route of infection remained unknown despite careful history taking. In adult patients with no apparent source of infection the virus was acquired mostly from sexual contact [19]. In children with an undetermined source however, the most probable route of infection was environmental, i.e., from close contact with another HBV carrier in day-care centers or elementary school.

Most of the study children were asymptomatic and were diagnosed during routine examinations. A large proportion of the children (27%) was examined because of abdominal pain, although it should be emphasized that this symptom might not be directly related to the hepatic disease in all cases.

Due to the multicenter nature of this retrospective study and the changes in treatment guidelines during the period it covers, there was no standard treatment protocol in our study: 3 mU/m^2 was given to 17 of the 38 children (45%) and 5–6 mU/m^2 to 21 (55%). However, the differences in dosage and duration between the protocols were minor. No differences in response rate were found in patient subgroups with varying IFN dose or duration of therapy.

The rate of complete response to IFN in our patients was 31.5% (12/38). This result is consistent with the results of several trials evaluating IFN therapy in Caucasian children with hepatitis B, which showed a response rate of 20–57% [7–14]. In contrast, one study performed in the Far East reported a much lower response rate [6]. A large proportion of our patients comprised children of Eastern

European origin whose response rate was similar to that of the Caucasian children in the studies mentioned above. A possible explanation for the relatively high response rate could be the high frequency of horizontal transmission. Infection through intrafamilial and interpersonal relationships is common in less endemic countries and could be associated with better response. The results of earlier studies on IFN therapy in children are summarized in Table 4.

Certain factors have been shown to be predictors of good response: younger age [12], high level of ALT or AST at diagnosis [10,20], low concentration of serum HBV DNA [21], female gender [14], and histological activity [9]. In our study, the low response rate to treatment could be attributed to the relatively high median age (10 years) compared to the findings of Ruiz-Moreno et al. [8] and Narkevicz et al. [12], who achieved better results with younger patients. Another study group, in which the median age was 12 years, showed a lower response to therapy [9]. The transaminase levels prior to initiation of therapy is known to be one of the crucial predicting factors of response. Sokal et al. [14], in a large multicenter prospective study, were the first to show that ALT and AST levels before treatment did not affect the response rate. Our results were similar: we found equal mean ALT values before treatment in both responders and non-responders.

One factor predicting good response to IFN identified in our study was infection through blood transfusion. The total number of our study population is too small to arrive at firm conclusions, although it is larger (51 patients) than those of most other pediatric studies [Table 4] [6,9,12]. Furthermore, a significant statistical correlation could be achieved. Alternatively, a factor predicting a poor response was superinfection or co-infection with hepatitis D virus: none of the four patients with HDV responded to IFN treatment, which is in agreement with the findings of Bortolotti et al. [22]. It is possible that those patients could have responded better to a higher dosage of IFN.

The side effects of IFN in our patients were relatively mild, and identical to previous reports [20]. The most common side effect of IFN was fever, usually below 38°C, appearing shortly after the interferon injection and disappearing after paracetamol ingestion. This phenomenon invariably occurred only after the first few injections. Other common side effects were weakness, fatigue, headache and other flu-like symptoms. Three children developed transient leukopenia.

In conclusion, we provide evidence that IFN therapy in children with chronic hepatitis B is efficacious in a considerable proportion of the cases and that it is free of major side effects. The response rate in our study was not affected by histology nor by the transaminase levels, although they are considered predictors of favorable response in adults. Therefore, the probability of patient response to therapy could not be predicted. Moreover, in view of the severe expected long-term complications of chronic hepatitis B in children, together with the mild side effects of IFN characteristic of this age group, we contend that all affected children could be considered candidates for IFN therapy, regardless of their ALT/AST levels or histology.

Table 4. Response to interferon therapy

Authors [ref]	Treated patients	Control group	Ethnic background	Complete response		Follow-up (mo)
				Treated patients	Control	
Lai [6]	12	12	Asian	17%	17%	18
Ruiz Moreno [7]	12	12	Caucasian	33%	25%	18
Ruiz Moreno [8]	24	12	Caucasian	50%	17%	15
Utili [9]	10	10	Caucasian	20%	10%	18
Sokal [10]	29	25	Caucasian	31%	0%	12
Barbera [11]	40	37	Asian & Caucasian	25%	13.5%	18
Narkewicz [12]	9	0	Caucasian	57%	-	12
Gregorio [13]	64	31	Caucasian	37.5%	13%	18
Sokal [14]	70	74	Caucasian	26%	11%	12

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