The Long-term Evolution of Chronic Hepatitis B Acquired in Childhood

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Abstract

The aim of this study was to assess the long-term evolution of chronic hepatitis B acquired in childhood. Methods: The study was carried out in 2007 - 2008 on a group of 77 adult patients who were diagnosed with chronic hepatitis B in childhood. The actual assessment included epidemiological, clinical, biological and virological data, ultrasound examination in all patients and liver histology in 3 patients. Results: From the 77 patients, 69 were HBeAg positive and the other 8 patients were anti-HBe positive when the diagnosis was made in their childhood. Thirty-seven patients from the HBeAg positive group and 2 patients from the anti-HBe group had been treated in childhood with IFN-α and the other 38 patients remained untreated (32 patients with HBeAg positive and 6 patients anti-HBe positive). Overall, 78.26% seroconverted to anti-HBe (87.50% untreated and 70.27% of patients treated with IFN). After a median follow-up period of 13 years, 36 patients from the HBeAg positive group (48.65% of treated patients and 56.25% of untreated ones) became inactive carriers. Seroconversion to anti-HBs, in the HBeAg positive group, occurred in 10.14% of cases (8.1% in treated patients) without statistical significance. Three patients from the whole group developed cirrhosis but none developed hepatocellular carcinoma. Conclusion: The long-term outcome in our patients with CHB acquired in childhood did not differ between treated and untreated patients.

Key words


Introduction

Chronic hepatitis B (CHB) is a major health problem: 350 million individuals are chronically infected with HBV worldwide [1]. Infection acquired in childhood is responsible for the majority of chronic HBV hepatites in adults, leading to complications in a significant number of cases: cirrhosis and hepatocellular carcinoma (HCC) [2]. In patients with CHB acquired in childhood several factors associated with the progression of liver disease were identified. These factors include high levels of viral load, genotype C of hepatitis B virus (HBV), viral mutants and the older age at HBeAg seroconversion [3]. The persistence of HBeAg was associated with an increased risk for progression to HCC [4]. There are other factors associated with the progression of CHB such as high levels of ALT, HBV/HCV and HBV/HDV coinfections, repeated HBV reactivations, the consumption of alcohol and associated comorbidities [5].

The natural history of CHB in children is characterized by an annual spontaneous hepatitis Be antigen (HBeAg) clearance rate lower than 2% during the first 3 years of life and up to 70% of children may seroconvert to anti-HBe later in childhood and adolescence (annual seroconversion rate, 5–15%) [6, 7]. So far, IFN-α and lamivudine have been used to treat children with CHB and have proved efficient in accelerating HBeAg seroconversion, particularly in children with higher baseline aminotransferase levels [8, 9]. It seems that for the HBV infection acquired during childhood, the long-term cumulative seroconversion rate of HBeAg does not differ between treated and untreated patients [7]. The children and young adults manifest a mild CHB. The long term outcome of the chronic HBV infection in children who respond to treatment as compared with that of the non-responders, and the spontaneous evolution of the infection is still unknown [10].

The aim of this study was to assess the long-term evolution of chronic hepatitis B acquired in childhood, either spontaneous or treatment-induced.

Methods

The study was carried out in 2007 and 2008 on a group of
77 adult patients aged between 18 and 33 who were diagnosed with CHB in childhood or adolescence (between the ages of 1 and 17). They were identified from a total of 250 children with CHB admitted to the 1st and 2nd Paediatric Clinics, Cluj-Napoca, between 1989 and 2003. The patients received a letter of information in which they were invited to report to the outpatient clinic of the Gastroenterology Department, 1st Medical Clinic, Cluj-Napoca for a basic check up related to their personal medical history. The initial data were used to collect information on infection, biochemical and virological aspects, the histological evaluation and the administered treatment. The exclusion criteria included the presence of concomitant systemic diseases, concurrent hepatitis C virus, hepatitis delta virus, HIV infection, other liver diseases (Wilson disease, autoimmune hepatitis, α-1-antitrypsin deficiency), and the consumption of toxic substances (any long-term medication, in particular). An informed consent was obtained from all patients.

On examination, the patients’ medical history, the route of HBV infection and the age when the infection was first diagnosed were recorded. Blood biochemical tests, serological HBV markers, viral markers and ultrasonographic examinations were carried out. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were evaluated using standard methods (upper limit of normal, 50 IU/L). The viral markers (HBsAg, anti-HBs, HBeAg, and anti-HBe levels) were measured by using the ELISA method. Serum HBV DNA level was quantitatively assessed with a commercial PCR assay (real-time PCR, Abbott Diagnostics), the cut-off value being 51 copies HBV DNA/mL. Alpha-fetoprotein level was assessed in all patients. Abdominal ultrasonography evaluated the liver, biliary tract, spleen, and portal vein. Liver biopsy was performed only in 3 patients who completed the criteria for inclusion in the antiviral treatment, after receiving informed consent. The other patients did not accept biopsy. The histopathological results were analyzed by using Knodell and Ishak score.

Terminology, definitions and the diagnosis criteria were established in accordance with AASLD guidelines 2007. An inactive carrier state was defined as having a detectable HBsAg level, an undetectable HBeAg level, a detectable anti-HBe level, a serum HBV DNA level < 10⁴ copies/mL, and persistently normal ALT and AST levels. The patients with CHB HBeAg positive were defined as having detectable HBsAg level, a detectable HBeAg level, an undetectable anti-HBe level, a serum HBV DNA level > 10⁴ copies/mL, normal or high levels of transaminases. The patients with CHB HBeAg negative were defined as having detectable HBsAg level, an undetectable HBeAg level, a detectable anti-HBe level, a serum HBV DNA level > 10⁴ copies/mL, normal or high levels of transaminases. A cured hepatitis B was defined as previous HBV infection, with undetectable HBsAg level, normal ALT level, and undetectable serum HBV DNA level. Liver cirrhosis was diagnosed by means of clinical and ultrasonographic criteria, and by histopathological examination in some of the patients.

The results were expressed in figures and percentages. The Epi Info 6 statistical program (χ² test) was used in order to assess the statistical significance of our results. The P value < 0.05 was considered as statistically significant.

**Results**

The study was carried out on a group of 77 adult patients (49 male, 28 female) aged between 18 and 33 who were diagnosed with CHB in childhood or adolescence. The evolution of CHB was evaluated after an average period of 13 years (6-20 years) from the initial diagnosis. The baseline characteristics of the patients with CHB are presented in Table I.

| Table I. Characteristics of 77 patients with chronic hepatitis B |
|-------------------|-----------------|-------------------|
| Characteristics   | Treated patients* (n=39) | Untreated patients** (n=38) |
| Gender, M/F       | 26/13           | 23/15             |
| Mean age at present (range) | 22.5 (18-27) | 25.5 (18-33) |
| Route of infection |                 |                   |
| Vertical          | 4               | 3                 |
| Horizontal        | 35              | 35                |
| Mean age at the first diagnosis (range) | 9.5 (2-17) | 9 (2-16) |

* Patients treated with antiviral therapy (IFN-α); ** Patients not treated with antiviral therapy

The suspected route of infection was percutaneous exposure (reused needles) in 70 patients. Vertical transmission was suspected in 7 children (Table I).

From the 77 patients, 69 patients were found HBsAg and HBeAg positive and 8 patients were anti-HBe positive when the diagnosis was established in their childhood (Fig. 1). Thirty-seven patients from the HBeAg positive group and 2 patients from the anti-HBe group were treated in childhood with IFN-α, 3-5 Mil IU 3 times per week for 4-6 months. The other 38 patients remained untreated.

Patients were selected for IFN therapy in childhood according to the following criteria: HBsAg and HBeAg positive on more than 2 occasions at least 6 months apart for all the patients, serum aminotransferases of at least two times the upper limit of normal; necrotic-inflammatory activity evidenced in liver biopsy samples. All treated patients had had a liver biopsy after receiving informed consent from the parents. Specimens were scored with regard to hepatitis activity (grades, 0–18) and fibrotic changes (stages, 0–6), according to Ishak score. Histological assessment revealed in treated patients mild and moderate hepatitis in 37 patients and severe hepatitis in 2 patients, who later developed cirrhosis. The liver cirrhosis was diagnosed by abdominal ultrasound and histological examination. Six patients HBeAg positive who did not respond to therapy with IFN-α received lamivudine for another 2 years, but they still maintained HBeAg positive.

The evolution of the 37 treated patients is presented in Fig. 2. On reassessment, 10 patients (27.03%) had CHB.
The long-term evolution of chronic hepatitis B acquired in childhood

HBeAg positive. Among these 10 patients, 3 patients had ALT level two times the upper limit of normal and HBV DNA $> 10^5$ copies/ml. Histological assessment revealed moderate hepatitis in 2 patients and mild hepatitis in one patient. For these 3 patients antiviral therapy was recommended. The other 7 patients with CHB who were HBeAg positive had normal ALT level and HBV DNA $> 10^5$ copies/ml. In 5 patients (13.5%) despite the seroconversion to anti-HBe and normal ALT levels, the HBV DNA level was higher than $10^5$ copies/ml; these patients having a HBeAg negative (mutant virus) CHB. Eighteen patients (48.65%) achieved seroconversion to anti-HBe, with HBV DNA $< 10^4$ copies/ml and normal levels of ALT (inactive carrier state). One patient (2.70%) from the treated patients developed cirrhosis. The seroconversion to anti-HBs (resolved hepatitis) was observed in 3 patients (8.1%).

The evolution of the 32 untreated patients is presented in Fig. 3. Among these, 10 patients had had liver biopsy in their childhood. Histological assessment revealed minimal hepatitis in all these patients. On reassessment, 4 patients (12.5%) had CHB HBeAg positive, with DNA HBV $> 10^5$ copies/ml and normal ALT levels. In 5 patients (15.63%) despite the seroconversion to anti-HBe and normal ALT levels, the HBV DNA level was higher than $10^5$ copies/ml; these patients having a CHB HBeAg negative. Eighteen patients (48.65%) became inactive carriers. One patient (3.12%) developed cirrhosis. In 4 patients (12.50%), the seroconversion to anti-HBs was observed.

Among the anti-HBe positive patients, 6 patients became inactive carriers, one patient achieved clearance of HBsAg, and one developed cirrhosis (Fig. 4).

Monitoring of α-fetoprotein levels and ultrasonographic examination did not reveal signs of HCC in any of the patients.

Overall, 78.26% seroconverted to anti-HBe (87.50% of untreated and 70.27% of patients treated with IFN). Seroconversion to anti-HBs occurred in 10.14% of cases (8.1% in treated patients). Our findings are important although the differences were not statistically significant possibly due to the small number of cases analyzed: P=0.54

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![Diagram](image1.png)

**Fig 1.** Flow chart of the 77 patients with CHB acquired in childhood.

![Diagram](image2.png)

**Fig 2.** Flow chart of the 37 patients with HBeAg positive chronic hepatitis B (CHB) treated with IFN-α
in patients with “s” seroconversion, and 0.08 in those with “e” seroconversion.

At the final evaluation we indentified 3 patients with CHB who were proposed for antiviral treatment. The other patients with CHB were included in monitoring programs according to AASLD guidelines.

**Discussion**

Our study adds information regarding the long-term outcome of CHB acquired in childhood. We observed that the leading mode of HBV transmission was horizontal in the majority of the patients (90.9%). Previous studies have shown that chronic HBV infection in eastern Europe is related to HBV transmission during childhood, mainly by therapeutic injections via nonsterilized needles and from chronically infected family members [12, 13].

The IFN-α dose and the duration of therapy were different from those recently recommended in the AASLD guidelines (6 MU/m²/dose) [11], according to the guidelines established at that time at national level in Romania.

All our treated patients (39 patients) and some of those untreated (10 patients) had had a liver biopsy in childhood. Histological assessment revealed mild and moderate hepatitis in the treated patients and minimal hepatitis in the untreated ones. Only the patients with mild and moderate hepatitis received antiviral treatment and the others remained untreated.

At the final evaluation of the 69 patients with CHB HBeAg positive, 48.65% from treated patients and 56.25% from untreated patients became inactive carriers. The HBsAg seroconversion to anti-HBs, was found in 8.1% of the treated patients and in 12.5% of the untreated patients. In our patients, the HBsAg seroconversion to anti-HBs after IFN matched the results of another study carried out in Romania, which indicated a 7.25% rate of HBsAg seroconversion [14]. The percentage of patients, who had undergone HBeAg seroconversion in our study, was slightly higher than the one reported in previous studies from our country [15]. In our study the spontaneous evolution of the CHB infection was found to be better than that under antiviral treatment although not statistically significant. In other studies, a high rate of seroconversion to anti-HBe up to 70% during childhood and adolescence was reported in children infected with HBV. HBV genotype may play an important role in the progression of HBV-related liver disease [16, 17]. In Romania, preliminary data about HBV genotype suggested a prevalence of A and D genotype. Genotype A was associated with an inactive carrier state, and genotype D with an active viral infection and with the evolution to HCC [18].

The HBeAg persistence was observed in 10 (27.03%) of the treated patients, and in 4 (12.5%) of the untreated
ones. Six patients who still had HBeAg positive after IFN therapy received lamivudine for 2 years, but did not obtain HBeAg seroconversion.

Among the patients with CHB HBeAg positive, 5 patients (13.51%) from the treated group and 5 patients (15.63%) from the untreated one, in spite of the seroconversion of the HBeAg to anti-HBe, had HBV DNA levels > 10^4 copies/ml and normal ALT levels.

Our results are similar to those reported by Iorio et al [11]. One hundred and eight patients with CHB acquired in childhood were studied. After a median period of observation of 12.1 years, 56% of the patients in the treated group became inactive carriers, 9.8% seroconverted to antibody to HBsAg, 14.8% had HBeAg positive CHB and 4.8% HBeAg negative CHB. In the untreated group, 48.4% became inactive carriers, 9.7% achieved clearance of HBsAg, 25.9% were HBeAg positive CHB and 4.8% HBeAg negative. None of the patients developed cirrhosis or HCC.

The natural history of chronic hepatitis B from childhood to adult life has not been fully elucidated. Cirrhosis and HCC due to HBV infection has been described rarely in childhood and is more frequent in the second decade of life [19, 20]. Although seroconversion seems to confer favourable outcomes in children with HBV infection, Bortolotti et al [21] reported 2 cases of HCC, 9 and 16 years respectively after seroconversion to anti-HBe. One of these two patients even had HBsAg seroconversion. The final evaluation of the 97 patients included in this study revealed that 91% of the untreated patients and all of the treated HBeAg-positive patients had become inactive HBsAg carriers. In our study, 3 patients (3.89%) developed cirrhosis and none developed HCC (in a follow-up period of 6 to 20 years from the first diagnosis, at actual age of 18-33 years, respectively). It is known that the risk of developing major complications of HBV infection is correlated with the duration of the infection and these complications tend to appear over 40 years of age [12].

In another study, Bortolotti et al [22] found liver cirrhosis in 3% of the patients. Previous studies reported that cirrhosis affected preferably young males and was associated with early biochemical remission and seroconversion of HBeAg to anti-HBe [23, 24]. Two of our 3 patients who developed cirrhosis were males.

Unfortunately, we did not have virological data (HBV-DNA serum levels) of the patients at the time of diagnosis of CHB, because at that time the test was not available in Romania. Bortolotti et al [25] reported low levels of HBV DNA which persisted for years in children with CHB after HBeAg seroconversion and remission of the disease, and even after HBsAg seroconversion. Indeed, minimal levels of HBV DNA have been reported to persist in at least half the children or adolescents for 10 years or more after HBeAg seroconversion to anti-HBe and biochemical remission [26]. The long-term persistence of HBV DNA in such cases could allow reactivation after a certain time period; it could explain occasional ALT elevations and it may contribute to the development of HCC. The selection of HBV mutants might also explain the persistently low levels of HBV DNA as well as the ALT abnormalities after HBeAg seroconversion to anti-HBe in some patients.

Ruiz-Moreno et al [27] reported that 95% of their patients had HBV DNA positive by PCR, and all of them were HBsAg positive even 12 years after seroconversion to anti-HBe. Chang et al [28] reported that children with CHB might achieve a normalization of ALT and absence of histologic activity, but seroconversion of HBeAg to anti-HBe is not necessarily an indicator of favourable prognosis, because cirrhosis or even HCC might develop in a small proportion of these children.

In conclusion, the long-term outcome in patients with CHB acquired in childhood did not differ in our treated patients from those untreated. We consider that this somewhat surprising finding necessitates further study on the long-term outcome of CHB acquired in childhood in treated and untreated patients. A better understanding of the evolution profile and factors interfering with this long-term evolution are crucial for selecting the appropriate time for treatment initiation, the eligible patients and the adequate antiviral agent.

Conflicts of interest

Nothing to declare.

References


18. Available at: http://www.icfundeni.ro/imuno_pr.htm


