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Autoantibodies in children with chronic hepatitis B infection and the influence of interferon alpha

Kronik hepatit B enfeksiyonu olan çocuklarda otoimmun antikor pozitifliği ve interferon alfa tedavisinin etkisi

Aydan KANSU, Zarife KULOĞLU, Fulya DEMİRÇEKEN, Nurten GÎRGÎN

Ankara University, School of Medicine, Department of Pediatrics, Division of Gastroenterology, Ankara

Background/aims: *One of the serious side effects of interferon-a (IFN) is the possible induction of autoimmunity. However, data concerning children with chronic hepatitis B (HBV) infection is limited with conflicting results. The aim of this study was to evaluate the frequency of autoantibody positivity in children with chronic HBV infection and to assess whether IFN treatment has any influence on exacerbation of serological or clinical parameters of autoimmunity.* ***Methods:*** *61 children (32 female, mean age 7.5±3.8 years) were evaluated in two groups. Group I (29 patients) received 5xlO^6 U/m^2 IFN-α and group II (32 patients) lOxlO^6 U/m^2 IFN-α three times per week for six months. Autoantibody levels (anti-TPO, anti-Tg, AMA, ASMA, LKM-1, ANA, ds-DNA) and Ig G, A and M were analyzed before and after IFN treatment and 12 months after completion of therapy.* ***Results:*** *No significant difference in autoimmune antibody positivity rate was observed between the two groups when compared at the beginning of the study and at the end of IFN treatment separately. SMA positivity rate was shown to significantly increase in group I after treatment was completed (p<0.05). None of the patients positive for autoantibodies showed further laboratory or clinical signs of autoimmunity. Thyroid hormones were within normal range in patients positive for anti-thyroid antibodies; however, thyrotropin-releasing hormone (TRH) stimulation test revealed subclinical hypothyroidism. All antibodies disappeared 12 months after completion of therapy. Overall, autoantibody positivity, pre- and posttreatment, were 16.3% and 54%, respectively (p<0.05). Age, sex, hepatitis activity index (HAI) score, HBV load and the dose of IFN had no influence on autoantibody formation. Complete and sustained response rates were similar in children with and without autoantibody.* ***Conclusions:*** *Autoantibody formation may occur in children with chronic HBV infection. IFN treatment leads to significant autoantibody formation, but this causes no organ dysfunction except for antithyroid antibodies associated with subclinical hypothyroidism. These results suggest that neither the presence of autoantibodies in choronic hepatitis B nor their development during IFN therapy is associated with severe autoimmune disorders in children with chronic HBV infection.*

Keywords: Interferon, chronic hepatitis B infection, children, autoantibody

Amaç: *Interferon a (IFN) tedavisinin ciddi yan etkilerinden biri de otoimmunitenin tetiklenebilmesidir. Ancak kronik hepatit B'li (HBV) çocuklarda bu konuda fazla veri yoktur ve sonuçlar tartışmalıdır. Bu çalışmanın amacı, kronik HBV enfeksiyonu olan çocuklarda otoantikor pozitifliğinin sıklığını araştırmak ve IFN tedavisinin otoantikor gelişimi ve klinik bulgular üzerine katkısının olup olmadığını belirlemektir.* ***Yöntem:*** *61 çocuk (32 kız, ort. yaş 7.5 ± 3.8 yıl) iki grupta incelendi. Grup Ve (29 hasta) IFN- a5x 10^6 U/m^2 dozunda, grup IFye (32 hasta) IFN-a 10x 106 U/m^2 dozunda, haftada 3 gün 6 ay süre ile uygulandı. IFN tedavisi öncesi, IFN tedavisi sonrası ve tedavi bitiminden 12 ay sonra antikor düzeylerine (anti-TPO, anti-Tg, AMA, ASMA, LKM-1, ANA, ds-DNA) ve Ig G, A and M düzeylerine bakıldı.* ***Bulgular:*** *Tedavi öncesi ve tedavi sonrası gruplar arasında antikor pozitiflik oranı bakımından anlamlı faklılık saptanmadı. Grup Tde SMA pozitifliğinin tedavi sonrasında anlamlı olarak arttığı görüldü (p< 0.05). Otoantikor pozitifliği gösteren hastaların hiçbirinde klinik ve labarotuvar olarak otoimmunite bulguları yoktu. Antitiroid antikorları pozitif bulunan hastalarda tiroid hormonları normal sınırlardaydı; ancak TRH uyarı testi ile subklinik hipotiroidizm olduğu gösterildi. Tedavi kesiminden 12 ay sonra tüm otoantikorlar negatifleşti. Tüm hastalar ele alındığında, toplam otoantikor pozitifliği tedavi öncesi %16.3 iken tedavi sonrasında % 54 bulundu (p<0.05). Otoantikor oluşumu ile yaş, cinsiyet, HAI skoru, HBV yükü ve IFN dozu arasında anlamlı bir ilişki bulunmadı. Otoantikor pozitifliği olan ve olmayan çocuklarda tam ve kalıcı cevap oranları birbirine benzerdi.* ***Sonuç:*** *Kronik HBV'li çocuklarda otoantikor gelişebilir. IFN tedavisi antikor oluşumunu artırmakla birlikte subklinik hipotiroidizm ile ilişkili antitiroid antikorları dışında herhangi bir organ disfonksiyonuna neden olmamaktadır. Bu sonuçlar kronik hepatit B enfeksiyonun gidişi sırasında ya da IFN tedavisi ile otoantikor gelişiminin olabileceğini ancak bu durumun ciddi otoimmun hastalıklara yol açmadığını göstermiştir.*

Anahtar kelimeler: Interferon, kronik hepatit B enfeksiyonu, çocukluk çağı, otoantikorlar

Address for correspondence: Aydan KANSU
Ankara University, School of Medicine, Department of Pediatrics, Division of Gastroenterology, Ankara

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INTRODUCTION

In children with chronic hepatitis B infection, interferon (IFN)-α currently the most effective treatment (1). Its most common adverse effect, the influenza-like syndrome, is self limited and usually disappears after the first few doses. Other common side effects are anorexia, transient weight loss, diarrhea, and mild bone marrow suppression (2). IFN-α also has a potentially severe side effect, such as induction of autoimmunity, which ranges from the appearance of tissue autoantibodies to overt autoimmune diseases (3, 4). It is reported that autoantibody positivity, which may be observed after IFN therapy, is sometimes sustained in the long-term (2). In the natural course of hepatitis C virus (HCV) infection, high prevalence of autoantibody positivity has been reported and, specifically, there are several reports concerning induction of autoimmune thyroid disorders by IFN therapy (5, 6, 7). It has also been suggested that in adult patients with chronic hepatitis B virus (HBV) infection, IFN-α treatment may induce the appearance of serological markers of autoimmunity or may even trigger the clinical manifestations of autoimmune hepatitis (8, 9). It is reported that high-dose IFN or prolonged therapy (>16 weeks) in chronic viral hepatitis may enhance the risk of immune-mediated phenomena through the immunomodulatory mechanism of IFN- (10). In children with chronic HBV infection, the presence of serological markers of autoimmunity has been investigated in two pediatric series (11, 12). In these series, the reported prevalence of autoantibody ranges from 12% to 34%, and it is suggested that IFN treatment does not induce clinically overt autoimmune disease, even in the presence of autoimmune serum markers. In these reports, standard dose (5 MU/ m^2) IFN was used for 3 to 12 months. To our knowledge, comparison of autoimmune serological markers in children with chronic hepatitis B who received high-dose and standard-dose IFN has not been investigated to date.

The aim of this study was to evaluate the frequency of autoantibody positivity in children with chronic HBV infection and to assess whether IFN therapy has any influence on exacerbation of serological or clinical parameters of autoimmunity and, if so, to compare the influence of high-dose and standard-dose IFN therapy in this regard.

MATERIALS AND METHODS

Sixty-one children with chronic hepatitis B infection (32 female, 7.5±3.8 years, range 2-18 years) were included. All patients were HBsAg- and HbeAg-positive, with HBV DNA > 5 pg/ml, alanine aminotransferase (ALT) level of 1.5 times higher than the reference values and/or liver histopathology compatible with chronic active hepatitis, and Knodell hepatitis activity index (HAI) >5. None of the patients had chronic systemic disease other than hepatitis B infection. All patients were negative for hepatitis D and C virus.

Patients were evaluated in two groups. Group I (29 patients) received 5 MU/m^2 IFN-alpha, and group II (32 patients) received 10 MU/m^2 IFN-alpha subcutaneously thrice weekly for six months.

Complete response to IFN treatment was defined as normalization of ALT, loss of HBV DNA and HBeAg and seroconversion of anti-HBe antibody after completing the therapy. Sustained response was defined as the continuation of the above condition one year after completion of therapy.

Autoantibody levels of thyroid peroxidase (TPO), thyroglobulin (Tg), anti-nuclear (ANA), anti-ds-DNA, anti-mitochondrial (AMA), smooth muscle (SMA) and liver-kidney microsomal-1 (LKM-1) autoantibodies and immunglobulins G, A and M were analyzed before and after IFN therapy. These autoantibodies were reanalyzed 12 months after the treatment was completed.

In those patients positive for anti-thyroid antibody, thyrotropin-releasing hormone (TRH)-stimulating test and thyroid function tests were performed.

HBsAg, HBeAg, anti-HBe and anti-HBs were detected using commercially available enzyme-linked immunosorbent assays (ELISA) (Abbott Laboratories, N. Chicago, IL). HBV DNA load was measured using hybrid Capture technique (Digene-Hybrid Capture System 4402-1060 M). ALT was measured by conventional methods (reference value 10-37 U/L).

Immunglobulin G, A and M levels, ANA, anti-DNA, SMA, AMA, LKM-1, thyroid hormones and thyroid antibodies were assayed by conventional methods. SMA, AMA and LMK-1 autoantibodies were accepted as positive if above 1:20 titers. Liver histological findings were interpreted using conventional criteria (13).

Statistical analysis

Results are expressed by mean±standard deviation (SD). Statistical significance was assessed using Mann-Whitney U, two-tailed Student's t-test and chi-squared methods (x^2 method).

RESULTS

Baseline clinical, biochemical and histological features were not different between the two groups (p>0.05) (Table 1).

Table 1. Baseline characteristics of group I and group II

	Group I (n=29)	Group II (n=32)	P
Sex (F/M)	15/14	17/15	>0.05
Age (year)	7.8±3.8	7.3±3.8	>0.05
ALT (U/L)	78.3±58.7	95.1±65.1	>0.05
HBV DNA (pg/ml)	1657±671.7	2100±876.2	>0.05
HAI (Knodell index)	6.3±2.3	6.9±2.4	>0.05
Lower socio-economic status	(%)	45 (80.4)	72 (80)

HAI: Hepatitis activity index

Autoantibody positivity and immunglobulin levels in groups I and II are shown in (Table 2). Immunoglobulin levels were within normal range in groups I and II both before and after therapy (p>0.05).

Table 2. Autoantibody positivity and immunglobulin levels in group I and group II

	Group I (n=29)		P	Group II (n=32)		P
	Before IFN	After IFN		Before IFN	After IFN	
Ig G (mg/gl)	1293.6±390.1	1533.8±404.9	NS	1290.7±294.3	1278.3±305.3	NS
Ig A (mg/gl)	129.2±49.6	131.4±77.3	NS	166.7±85.4	162.9±70.9	NS
Ig M (mg/gl)	175.8±163.7	137.1±75.8	NS	136.8±75.5	179.5±74.7	NS
ANA %, (n)	-	13.8, (4)	NS	9.4 , (3)	18.8, (6)	NS
Anti-ds DNA %, n	-	-	-	-		
AMA %, (n)	-	3.4, (1)	NS	3.1,(1)	3.1,(1)	NS
SMA %, (n)	6.8, (2)	34.4, (10)	<0.05	12.5,(4)	21.8, (7)	NS
LKM-1 % (n)	_	3.4, (1)	NS	-	-	NS
Anti-TPO %, (n)	-	3.4, (1)	NS	-	-	NS
Anti-Tg %, (n)	-	3.4, (1)	NS	-	3.1,(1)	NS

NS: Non significant, TPO: Thyroid peroxidase, Tg: Thyroglobulin, ANA: Anti-nuclear antibody, AMA: Anti-mitochondrial antibody, SMA: Smooth muscle antibody, LKM-1: Liver-kidney microsomal-1

None in group I and three patients in group II had ANA before IFN therapy. ANA appeared in four patients in group I and in three additional patients in group II. Antibody to ds DNA was detected in none of the patients in either group neither before nor after therapy. None in group I and only one patient in group II had AMA before IFN therapy. In group I, one patient developed AMA after IFN therapy. The most commonly found autoantibody in all patients before IFN therapy was SMA, which was positive in two and four patients in groups I and II, respectively. In these patients, SMA remained positive after IFN therapy. At the end of therapy, 11 additional patients (8 in group I and 3 in group II) were positive for SMA. The increase in SMA positivity in group I at the end of therapy was significantly different (p<0.05). Antibody to LKM-1 was negative in all patients before IFN therapy, but occurred in one patient in group I at the end of therapy. Anti-TPO and anti-Tg were negative in all patients before therapy. In group I, one patient each developed anti-TPO and anti-Tg in group I and in group II; one patient developed anti-Tg after IFN therapy.

In summary, the only significant difference noted was in SMA positivity in group I when comparison was made between the beginning and the end of IFN therapy (p<0.05). When the two groups were compared, antibody positivity rate was not significantly different before or after therapy (p>0.05).

Overall, autoantibody positivity was observed in 10 of 61 children (16.3%) before IFN therapy. At the end of treatment, autoantibodies were positive in 23 patients (45.1%) of 51 previously negative patients (p<0.05). Autoantibody positivity in all patients is shown in (Table 3). Three patients (4.9%) had ANA before IFN therapy and it appeared in an additional seven patients (13.7%) who were previously negative (p>0.05). Antibody to ds DNA was detected in none of the patients before or after IFN therapy. One patient (1.9%) had AMA

Table 3. Autoantibody positivity in **all** patients

	Before IFN (n=61)	After IFN (n=61)	P
ANA %, (n)	4.9, (3)	16.3 (10)	NS
Anti-ds DNA %, n	-	-	NS
AMA, % (n)	1.6, (1)	3.2, (2)	NS
SMA % (n)	9.8, (6)	27.8, (17)	<0.05
LKM-1 % (n)	-	1.6, (1)	NS
Anti-TPO, % (n)	-	1.6, (1)	NS
Anti-Tg, % (n)	-	3.2, (2)	NS
Overall positivity %, (n)	16.3, (10)	54, (33)	<0.05

NS: Non significant

before IFN therapy and remained positive. Another patient also developed AMA after IFN therapy was completed (p>0.05). The most commonly detected autoantibody in all patients before IFN therapy was SMA, which was found in six patients (9.8%). In these patients, SMA remained positive after IFN therapy. After treatment, 11 additional patients (21.5%) developed SMA (p<0.05). Antibody to LKM-1 was negative in all patients before IFN therapy and appeared in one patient (1.9%) after therapy (p>0.05). Anti-TPO and anti- Tg were negative in all patients before IFN therapy. After therapy, anti-TPO developed in one and anti-Tg developed in two patients (p>0.05). None of the patients positive for autoantibodies showed further laboratory or clinical signs of autoimmunity. Thyroid function tests were within normal range in three patients positive for anti-thyroid antibodies; however, TRH stimulation test revealed subclinical hypothyroidism in these patients. These patients did not require any treatment as they were clinically euthyroid.

All patients showing antibody positivities became negative when re-tested 12 months after completion of therapy.

Complete response was achieved in 16 patients (complete response rate 26.2%). In all of the complete responders, normalization of ALT levels, loss of HBeAg and seroconversion to anti-HBe as well as loss of HBV DNA were permanent throughout the one year after completion of therapy. One year after completion of therapy, eight patients in addition showed complete response. Thus, a sustained response rate was found in 24 patients (39.3%). Loss of HBsAg and seroconversion to anti-HBs occurred in two patients (3.2%). Anti-HBs seroconversion was seen during IFN therapy in one patient and one year after completion of therapy in the other patient.

Complete response and sustained response rates were 24.1% and 41.3% in group I and 28.1% and 37.5% in group II, respectively (p>0.05). Clinical, virological and biochemical features of patients with and without antibody postivity are shown in (Table 4).

Complete response was achieved in 4 of 10 patients who had autoantibody before starting IFN therapy, and these children were also sustained responders.

Complete response and sustained response were seen in 9 (27.2%) and 13 (39.3%) of 33 autoantibody-positive patients, respectively.

Seven (25%) of the 28 children who were negative for autoantibody achieved response. These patients remained responsive one year after completion of therapy. One year after completion of therapy, an additional four patients achieved complete response. Thus, sustained response was seen in 11 patients (39.2%).

Complete response and sustained response rates were not significantly different in autoantibody-positive and -negative children (p>0.05). Autoantibody positivity rate was also evaluated according to biochemical response (i.e. ALT normalization)

Table 4. Clinical, virological and biochemical features of patients with and without antibody positivity

	Antibody positive (n=33)	Antibody negative (n=28)	P
Age (year)	6.6±3.5	8.6±4.1	NS
Sex (Female/Male)	17/16	15/13	NS
ALT (mean U/L±SD) before therapy	112.7±82.8	70.1±35.1	<0.05
ALT (mean U/L±SD) after therapy	34.2±16.6	36.5±16.1	NS
HAI (mean (Knodell index)±SD)	7.1±2.7	6.2±2.1	NS
HBV DNA (mean pg/ml±SD)	1833.2±413.4	2281.2±1640.1	NS
IFN dosage	15	14	NS
5 MU/m^2 (n)	18	14	
10 MU/m^2 (n)			
Complete response rate (n), %	(9), 27.2%	(7), 25.%	NS
Sustained response (n), %	(13), 9.3%	(11), 39.2%	NS

NS: Non significant

at the end of IFN treatment. In 15 patients, ALT remained above upper normal limit; eight of them were positive for at least one autoantibody (53.3%). In 46 patients, ALT became normal at the end of IFN treatment. Autoantibody positivity was seen in 25 of them (54.3%) ($p>0.05$).

Age, sex, HBV load, HAI scores and dosage of IFN were not significantly different among patients with and without antibody positivity. At the beginning of therapy, ALT levels were significantly higher in the autoantibody-positive group than in the autoantibody-negative group ($p<0.05$). After IFN therapy, ALT levels were 34.2+16.6 U/L in the autoantibody- positive group and 36.5±16.1 U/L in the autoantibody-negative group, respectively, which was not significantly different ($p>0.05$).

DISCUSSION

Interferon-α is the most successful drug currently available for treatment of children with chronic hepatitis B infection (14, 15). The development of autoantibodies and autoimmune reactions has been reported with IFN therapy (6, 9, 16, 17). But there is little information about stimulation of autoimmunity by IFN therapy in children with chronic hepatitis B infection (11, 12). Prevalence of autoantibody positivity in adults with chronic hepatitis B infection varies from 0% to 38% (8, 18), whereas in children, it is reported to be from 12% to 34% (11, 12). The presence of autoantibodies in 16.3% of patients in our study is lower than that reported by Gregorio et al. (34%) (11), but similar to that reported by Muratori et al. (12%) (12). In adult patients with HCV infection, a strong correlation has been shown between non-organ-specific autoantibodies and biochemical and histological activity of liver disease (19), but it is unclear whether non-organ-specific autoantibodies are directly involved in the progression of the liver damage or whether they simply represent a physiological response to autoantigens released from dying hepatocytes (20). However, the cause or clinical significance of autoantibodies in the course of chronic HBV infection is still unknown. It has been suggested that production of autoantibody may be the result of molecular mimicry between HBV DNA polymerase and the antigenic targets of ANA and SMA (21). Moreover, IFN has been shown to increase the expression of major histocompatibility complex class II antigen, which may have a role in triggering autoimmune disorders (22).

It has been reported by Mayet et al. (8) that none of the adult patients with chronic hepatitis B infection had autoantibody before IFN therapy, but the majority of them developed at least one autoantibody during or after IFN therapy. In contrast, it was suggested that in children, autoantibody positivity is a part of the natural course of chronic HBV infection and that their prevalence and titer are unaffected by IFN therapy (11). Our data does not support this concept because we demonstrated that autoantibody prevalence was highly affected by the use of IFN. However, we showed that autoantibody formation was not influenced by high doses of IFN-α.

Muratori et al. (12) reported that only one of 19 treated children with chronic hepatitis B infection developed SMA. Contrary to this study, our results demonstrated that SMA developed significantly after IFN treatment, but none of these patients had any clinical sign of autoimmune disease.

Similar to reports of Gregorio et al. (11) and Muratori et al. (12), only one patient developed AMA and LKM-1 in our series.

There is controversy about the development of antithyroid antibodies in patients with chronic hepatitis B by IFN therapy. While Gregorio et al. (11) reported none, Mayet et al. (8) showed that 45% of their patients became positive. The difference in population characteristics and the dose of IFN used in the series of Mayet et al. probably accounts for the observed discrepancy (8, 11). In our study, thyroid autoantibodies appeared only in three patients (4.9%), one after high-dose and two after standard-dose IFN-α. None of these patients had overt thyroid dysfunction.

It has been suggested that patients who receive high-dose IFN have an increased likelihood of autoantibody formation (8). Contrary to the literature, we observed no correlation between development of autoantibody and the dose of IFN. In our study, among patients who were found positive for antibody, 15 had received 5 MU/m^2 IFN and 18 patients had received 10 MU/m^2 IFN. There are some case reports that suggest the possible development of autoimmune hepatitis triggered by interferon. Although the most commonly found autoantibody after IFN treatment in our patients was SMA, it was not found to be associated with manifest liver dysfunction, and these antibodies disappeared after cessation of IFN treatment. However,

mild thyroid dysfunction in the form of subclinical hypothyroidism was documented in our patients who developed antithyroid antibodies.

It has been reported that children with HCV infection were less likely to benefit from IFN therapy when they had autoantibodies (12). According to our data, presence of autoantibody before or during treatment did not cause any difference in the rate of complete or sustained response to IFN therapy.

Neither HBV load, HAI score, sex, age, nor the dose of IFN had any correlation with autoantibody formation. The only significant difference was in basal ALT levels, which were higher in patients who were positive for antibodies. However, autoantibody prevalence was not significantly different in patients with and without ALT normalization at the end of IFN treatment. We can argue that this data may suggest that despite autoantibody formation, IFN causes no serious immunologic damage.

In conclusion, antibody formation may occur in chronic HBV infection in children. In our study, we showed that IFN therapy leads to significant autoantibody formation without causing organ dysfunction, except for antithyroid antibodies associated with subclinical hypothyroidism. Moreover, we demonstrated that in all patients, autoantibodies disappeared one year after completion of treatment. We conclude that induction of autoimmune markers by IFN therapy did not affect the response rate in children with chronic hepatitis B. These results indicate that development of autoantibody before or during IFN therapy is not associated with severe autoimmune disorders in children with chronic hepatitis B infection and, in this regard, IFN therapy is safe and reliable in children with chronic hepatitis B infection.

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