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IMMUNOSUPPRESSION IS SAFE IN PATIENTS WITH AUTOIMMUNE HEPATITIS AND OCCULT HEPATITIS B

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ABSTRACT:

Background: Autoimmune hepatitis (AIH) is a leading cause of chronic liver disease treated by immunosuppression namely, corticosteroids and azathioprine. In autoimmune liver diseases, in addition to the most common overlap syndromes of AIH/primary biliary cirrhosis (AIH/PBC) and AIH/primary sclerosing cholangitis (AIH/PSC), an AIH/viral hepatitis (AIH/VH) variant is distinguished. Chronic hepatitis B virus (HBV) infection is a major global health problem despite the availability of an efficacious vaccine. It is an immunopathic virus. Occult HBV infection is a complex clinical entity documented worldwide. Occult HBV (OHB) infection was not recognized as a clinical entity until the early 1990s.

Aim of the work: The aim of the study was to investigate the presence of occult hepatitis B virus in patients with autoimmune hepatitis, and also, the risk of occult HBV reactivation was investigated in patients with AIH and occult HBV treated by immunosuppression.

Subjects and Methods: 150 subjects were included in the study and divided into two groups: Group I included 50 patients with autoimmune hepatitis with or without cirrhosis and Group II included 100 healthy control subjects negative for hepatitis C virus antibody (HCV Ab) and hepatitis B surface antigen (HBs Ag) of matched age and sex. Patients and controls were investigated for the presence of occult hepatitis B. Patients having both autoimmune hepatitis and occult HBV who needed to be treated with immunosuppression were followed up for occult HBV reactivation for one year.

Results: Presence of Occult HBV was found to b e statistically significantly higher in patients with AIH than in controls (P=0.016), but no significant difference was found between cirrhotic AIH patients and non cirrhotic AIH patients (P=0.384). None of AIH and occult HBV patients treated with immunosuppression showed reactivation of HBV during follow up period of one year.

Conclusions: Presence of occult HBV is much higher in patients with autoimmune hepatitis than in healthy subjects. Also, immunosuppression for patients having both AIH and occult HBV is safe.

Key words: *Occult hepatitis B, Autoimmune hepatitis, Immunosuppression*.

INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease which, if untreated, often leads to cirrhosis, liver failure and death. Autoimmune hepatitis was one of the first liver diseases for which an effective treatment was developed and the benefit proven by randomized controlled trials. Nonetheless, both the diagnosis and the treatment of autoimmune hepatitis remain full of challenges. The clinical spectrum is very wide, ranging from subclinical non-progressive disease to fulminant hepatic failure. Diagnostic criteria based on elevation of immunoglobulin G (IgG), demonstration of characteristic autoantibodies, and histological features of hepatitis in the absence of viral disease are very helpful. However, in some patients, diagnosis remains a clinical challenge. Adequately dosed steroids are the mainstay of remission induction treatment,while remission maintenance is best achieved by azathioprine.[1]

AIH is described as a disease of young women, the patient group in which the disease was initially reported. A female predilection has been confirmed in almost all studies with a female to male ratio of around 3:1 across the world. The age of manifestation of AIH varies greatly from as early as the first year of life up until the eighties.[2-5]

AIH has been categorized into two distinct disease subtypes based on the antibody profiles. Type 1 AIH is associated with the presence of either antinuclear (ANA) or anti smooth muscle (ASMA) antibodies in the serum and accounts for about 75% of patients.5-7 Type 2 AIH is associated with the presence of anti-liver kidney microsomal-1 (LKM-1) and anti-liver cytosolic-1 (LC-1) antibodies. [8-10]

In addition, 10-30% of patients with AIH have detectable antibodies to soluble liver antigen (SLA) or liver pancreas antigen (LP); these antibodies are specific for AIH, so may also be a useful adjunct in the diagnosis of type 1 AIH when conventional autoantibodies are negative.[11]

Controversy has existed in relation to the existence of a third subtype of AIH defined by the presence of anti-SLA/LP antibodies,[12] but these patients display the typical clinical and pathological hallmarks of type 1 AIH and should be treated as such.[13]

In autoimmune liver diseases, in addition to the most common overlap syndromes of AIH/primary biliary cirrhosis (AIH/PBC) and AIH/primary sclerosing cholangitis (AIH/PSC), an AIH/viral hepatitis (AIH/VH) variant is distinguished.[14]

According to European Association for the study of the liver (EASL), about one third of the world's population have serological evidence of past or present hepatitis B virus (HBV) infection, and more than 350 million people may be affected by chronic HBV infection.[15]

It is generally accepted that HBV is an immunopathic virus (the host's immune response rather than the virus itself is causing the hepatocellular damage).[16]

Patients with hepatitis B surface antigen (HBs Ag) detectable for six months or more are defined as having chronic hepatitis B.[17]

Healthy carriers are characterized by a positive HBs Ag that persists more than six months, but with normal liver enzymes values. They are negative for HBV e antigen (HBe Ag), and are associated with low or undetectable serum HBV deoxyribonucleic acid (DNA) and low risk for progression to cirrhosis or hepatocellular carcinoma (HCC).[18]

Owing to modern molecular analysis, the viral genome of HBV can persist indefinitely in previously infected HBs Ag-negative subjects.[17] This persistence occurs by conversion to a covalently closed circular HBV DNA (cccDNA) in the hepatocyte, which then binds to proteins, forming a mini chromosome. This cccDNA is the molecular basis of occult hepatitis B infection because to its stability and long-lasting persistence in the nuclei of hepatocytes.[19]

Anti-core IgM antibody is the first antibody to appear, even preceding HBsAg, and targets the nucleocapsid of HBV. Anti-core immunoglobulin G (IgG) can be found in almost every patient with a previous contact with HBV, even in HBV carriers without other responses. This serological pattern is called "anti hepatitis B core (anti-HBc) alone", and might reflect an occult HBV infection. Anti-HBc IgG is present in the different phases of hepatitis, including recovery, and may persists longer than anti-HBs or anti-HBe; however, it is not protective.20

Anti-surface antibody is the last antibody to appear (about three months after acute phase), and it is able to neutralize the virus. In vaccinated subjects it is the only positive marker. This antibody can be used with anti-HBc to study the serological status of patients with a probable occult HBV.[21]

The gold standard test for detection of occult infection is the amplification of HBV DNA. However, the serological assay for the long-lasting antibody response to the highly immunogenic HBV core antigen (anti-HBc) represents a qualified candidate as a surrogate for DNA amplification, or for increasing overall sensitivity when assessing the risk of occult hepatitis in peripheral blood. The risk of occult hepatitis associated with anti-HBc seropositivity has been demonstrated extensively, and the presence of antibody response to HBc can be considered a sentinel marker of occult HBV infection. In addition, anti-HBc determination is useful in occult HBV diagnosis, even when HBV DNA is available, because of the possibility of intermittent viremia.20,21

AIM OF THE WORK:

The aim of the study was to investigate the presence of occult HBV in patients with AIH, and also, the risk of occult HBV reactivation was investigated in patients with AIH and occult HBV treated by immunosuppression.

SUBJECTS AND METHODS:

We studied 150 subjects and was classified into two groups as follows:

Group I: **50 patients with autoimmune hepatitis** with or without liver cirrhosis and –ve for HCV Ab and HBs Ag.

Group II: **100 healthy control subjects of matched age and sex; they were** –ve for HCV Ab and HBs Ag.

All subjects were subjected to the following:

1. History taking and thorough clinical examination.

- Laboratory investigations22,23 including:
- liver profile in the form of prothrombin time and activity, serum albumin, and total and direct fractions of serum bilirubin concentrations.
- Liver enzymes in the form of alanine and aspartate aminotransferases (ALT, AST).
- Serum alfa fetoprotein (AFP).
- Fasting blood glucose, blood urea, and serum creatinine.
- Serum hepatitis-C virus antibodies and serum hepatitis-B virus surface antigen (HBsAg) using enzyme immunoassay.
- HBc IgG and HBs Ab. Occult HBV defined as +ve HBc IgG and –ve HBs Ab.
- Autoimmune markers namely; ANA, ASMA, LKMA, anti mitochondrial antibody (AMA), and total IgG.

Cirrhotic patients will be scored according to Child-Pugh classification.24

- Polymerase Chain Reaction (PCR) was done for patients with AIH undergoing immunosuppression and scheduled as basal on start of treatment and every three months for one year along with testing for HBs Ag and HBc IgM.
- Occult HBV reactivation was defined as HBs Ag seroconverion from –ve to +ve, HBc IgM +ve, HBV DNA elevation from the base line level.25
- Abdominal ultrasound was done for all patients.

Any patient with hepatocellular carcinoma, diabetes mellitus, malignancy, renal failure, or collagenic disease was excluded.

The treatment schedule for patients having indication for treatment of AIH was as follow(9): Azathioprine 50 mg daily and prednisolone with starting dose of 30 mg daily decreasing over one month to 10 mg maintenance dose for two years in case of remission.

STATISTICAL METHODS:

Data were collected, revised and transferred into statistical package for social science (SPSS/ version 11.5). Quantitative data like age was presented as mean (±SD), and t test was used to test for difference in mean age between the two study groups.

The association between AIH and occult HBV, and presence of cirrhotic AIH with occult HBV was tested using Chi Square test.

A level of 5% was considered as the cutoff level of significance.

Ethics:

All participants were asked to freely volunteer to the study and informed written consent was gathered prior to their inclusion in the study protocol, according to the ethical guidelines of Medical Research Institute, Alexandria University.

RESULTS:

As regarding demographic data, there was no statistically significant difference between the two studied groups regarding age (P=0.506), gender (P=0.306), or residency (P=0.231).
In AIH group, 28% of patients had liver cirrhosis and 96% were type I AIH and 4% were type II AIH.

Presence of occult hepatitis B virus was found to be statistically significantly higher in AIH patients (14%) than in healthy control subjects (3%) (P=0.016) (Table 1). However, no statistically significant difference was found between cirrhotic and non cirrhotic AIH patients regarding presence of occult HBV (21.4% Vs 11.1% with P= 0.384) (Table 2).

Five out of seven patients with AIH and occult HBV needed to be treated with immunosuppression by corticosteroids and azathioprine as previously mentined in subjects and methods. None of them showed manifestations of occult HBV reactivation through the follow up of one year.

Table 1: prevalence of occult HBV in the studied groups

	AIH group (n=50)	Control group (n=100)	X^2	P
Occult HBV %				
Yes	(7) 14%	(3) 3%	4.835	0.016
No	(43) 86%	(97) 97%		

Table 2: prevalence of occult HBV in cirrhotic Vs non cirrhotic AIH patients.

	Cirrhotic AIH patients (n=14)	Non cirrhotic AIH patients (n=36)	X^2	P
Occult HBV %				
Yes	(3) 21.4%	(4) 11.1%	0.240	0.384
No	(11) 78.6%	(32) 88.9%		

DISCUSSION:

Autoimmune hepatitis (AIH) is an unresolving progressive liver disease that affects preferentially females and is characterized by interface hepatitis, hypergammaglobulinaemia, circulating autoantibodies and a favorable response to immunosuppression.[26-28] Due to the absence of a specific marker of the disease and the large heterogeneity of its clinical, laboratory and histological features, AIH diagnosis may be difficult. Therefore, the International AIH Group (IAIHG) met for the first time some 20 years ago and proposed a cumulative score,[9] which was subsequently revised and simplified.[29]

The dominant hypothesis postulates that AIH is a disease developing in a genetically predisposed individual, who is also exposed to environmental factors. Thereafter, the autoimmune attack is perpetuated, possibly via molecular mimicry and is favored by the impaired control of regulatory T-cells.[30]

HBV is an immunopathic virus.[22] Occult HBV (OHB) patients are well demonstrated category of patients, and -ve HBs Ab along with +ve anti-HBc IgG could be used to diagnose this entity.[15,21]

Urbani *et al* [20] stated that, the risk of occult hepatitis associated with anti-HBc seropositivity has been

demonstrated extensively, and the presence of antibody response to HBc can be considered a sentinel marker of occult HBV infection.

Raika[31] stated thet, HBc Ab test is a practical screening method for OHB and is a surrogate marker of previous HBV infection in the immune competent patients and HBV DNA assay is an accepted alternative for OHB screening in the immunosuppressed individuals whose HBc Ab is in a low detectable titer.

Shouval et al[32] stated that, Patients with OHB should be monitored for alanine aminotransferase and HBV DNA during the course of immunosuppression.

In the present study, it was found that patients with AIH have more prevalent occult HBV (based on the presence of anti HBc IgG and absence of HBs Ab) than in healthy control subjects. This could be attributed to the nature of HBV as an immunopathic virus, which may lead to alteration of body immune system and can also lead to autoimmune diseases.

Going with our study, Georgiadou et al[33] found that a significant proportion of autoimmune liver disease patients have occult HBV compared with blood donors (P=0.000).

In our study, it was found that none of patients with AIH and occult HBV treated by immunosuppression using corticosteroids and azathioprine showed manifestations of occult HBV reactivation in a prospective study for one year.

For rituximab, a prospective study demonstrated that 2-year cumulative risk of reactivation of OHB found to be 41.5%, but prospective data is still lacking for other immunosupressive regimes. The optimal management in preventing HBV reactivation would involve appropriate risk stratification for different immunosuppressive regimes in HBsAg-negative, anti-HBc positive individuals.[(34)]

Elbedewy et al[35] concluded that anti-HBc screening is mandatory before chemotherapy and HBsAg-negative/anti-HBc-positive patients should be closely observed for signs of HBV reactivation through the regular monitoring of ALT. They recommended prophylaxis using lamivudine for anti-HBc positive patients before chemotherapy.

The difference between our results and the results of the last two studies could be attributed to the type of immunosuppressants.

Conclusion:

From this study we can conclude that patients with AIH have more prevalent occult HBV compared with healthy control subjects, and treatment by corticosteroids and Azathioprine in such cases is safe and doesn't increase risk of occult HBV reactivation.

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