# CHRONIC VIRAL HEPATITIS B AND HEPATIC LESIONS INDUCED BY ALCOHOL

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***Keywords:*** *hepatitis B virus, alcohol*

***Abstract:*** *The coexistence of a chronic hepatitis B and an alcoholic hepatopathy leads to a mixed hepatopathy where both factors have at least an additive effect, producing more severe hepatic lesions, with an important potential to evolve towards liver cirrhosis and hepatocellular carcinoma. The study was aimed at analyzing the main biological, virology and histopathological findings of the mixed hepatopathy (alcohol plus viral B). Two test groups were used, cases composed of patients with a mixed hepatopathy, and controls including patients with chronic hepatitis B. A comparative analysis was done on factors such as age, sex, viral strains involved, severity of fibrotic and necroinflammatory lesions, identifying lesions specific to the alcoholic aggression, the enzymatic profile, viral kinetics, specific features of the stages of the viral B infection when combined with an alcoholic aggression.*

***Cuvinte cheie:*** *hepatită, virală B, alcool*

***Rezumat:*** *Asocierea între hepatita cronică virală B şi hepatopatia etanolică duce la o hepatopatie în care cei doi factori de agresiune hepatică au un efect cel putin aditiv, în producerea de leziuni hepatice mai severe, cu potenţial evolutiv mai rapid spre ciroză hepatică şi carcinom hepatocelular. Studiul vizează principalele aspecte biologice, virusologice şi histopatologice ale hepatopatiei mixte, alcoolice şi virale B, comparativ cu hepatita cronică virală B. Sunt analizate comparativ pe un lot de pacienti cu hepatopatie mixtă, virală B şi alcoolică şi un lot de pacienţi cu hepatită cronică virală B aspecte privind vârsta şi sexul pacientilor, tipul tulpinilor virale infectante, severitatea leziunilor fibrotice şi necroinflamatorii, identificarea leziunilor specifice agresiunii alcoolice, profilul enzimatic hepatic şi cinetica virală, aspecte comparative ale fazelor evolutive ale infecţiei virale B sub influenţa agresiunii alcoolice*

## INTRODUCTION

A vast amount of epidemiological data indicates a higher prevalence of hepatitis viral infections in patients with a history of alcohol abuse. (1,2,3,4) Among alcoholic hepatitis patients an important role is attributed to the hepatitis B virus (HBV) infection, resulting in alterations of the natural course of both diseases, thus leading to the complex picture of a mixed hepatopathy, both alcoholic and B viral. (1,3)

## THE AIM OF THE STUDY

Our hypothesis was the existence of a mixed hepatopathy, both alcoholic and B viral, more severe than the chronic viral hepatitis B and with a more rapid progression towards cirrhosis and hepatocellular carcinoma. (1,2)

We analyzed the working hypothesis according to which the histological markers typical for alcoholic hepatitis (the macrovacuolar dystrophy or the pericentrilobular fibrosis) retain their specificity in the mixed etiology hepatitis. (5,6,7) By analyzing the histological data available we determined whether the main biochemical parameters tend to follow the alcoholic pattern or the viral one, something seen by us as being of utmost importance for the differential diagnosis. (5,6)

We also analyzed the way in which alcohol can influence the host-virus balance by determining the nature of the infection with HBV (wild or mutant virus) and by evaluating the viral load. (8)

## MATERIAL AND MERHOD

Our case group consisted of 34 patients with alcoholic hepatitis infected with hepatitis B virus. The inclusion criteria were age between 25 and 65 years old, at least 5 years of at least 80 grams/day alcohol intake in men and 40 grams/day in women in order to develop a significant degree of toxic hepatic damage (5) and the presence of HBV infection markers – total HBc antibodies, HBs antigen and detectable levels of HBV DNA. (6,7)

The exclusion criteria were infection with the hepatitis virus C or D, HIV, hepatic cirrhosis, autoimmune hepatitis, autoimmune cholangiopathy, hepatic thesaurismosis, congenital jaundice, biliary obstruction, diabetes, heart conditions leading to hepatic steatosis, obese patients (IMC>25).

Our control group consisted of 98 patients with chronic viral hepatitis B. The inclusion criteria were age between 25 and 65, the presence of HBV chronic infection markers - total HBc antibodies, HBs antigen and detectable levels of HBV DNA. (6,7)

The exclusion criteria for this group were alcohol intake over 20 grams/day for both men and women, age below 25 or over 65, non-viral hepatic pathology, hepatitis C or D, autoimmune, primitive or secondary biliary hepatitis, diabetes, obesity (IMC over 25), any disease having potential for liver stasis, hepatic thesaurismosis, congenital jaundice.

Alcohol intake was documented by medical history

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and using the CAGE and MAST (Michigan Alcoholism Screen Test) tests if needed. (5) We determined the most important biochemical data for chronic hepatitis B and alcoholic hepatitis (SGOT, SGPT and GGT). HBs antigen, HBe antigen and HBe HBV DNA for all patients. (5,6) The histological evaluation was performed by hepatic biopsy, the lesions being quantified according to the Knodell score. (5,7)

The database was generated using Microsoft Access And Microsoft Excel software and for the statistical analysis we used GraphPad InStat and Medcalc, considering $p<0.05$ as significant

## RESULTS

The mean age for the mixed hepatopathy (alcoholic plus B viral) compared to the lone B viral group showed a significantly higher value for the former group (49.26±2.86 compared to the control group 40.35±1.96, $p<0.0001$.

The higher mean age for the mixed hepatopathy group denotes an additive as opposed to synergic effect of the two aggressive factors and a prolonged exposure of alcoholic patients to risk factors for viral hepatitis infection, the prevalence of the infection growing higher with age.

The sex distribution for the mixed hepatopathy group compared to the lone viral B group shows a clear predominance for the male sex: 85.71% male/14.29% female in the cases vs. 65.31% male/34.69% female for the controls, the difference being statistically significant.

These findings actually fit the epidemiology of the alcoholic hepatitis, which is predominant in men, compared to the viral hepatitis B with a more balanced sex distribution.

We tested the hypothesis that the alcoholic aggression would favor one of the viral strains (wild or mutant) over the other. In the case group we found 74.28% being infected with a mutant viral strain compared to 75.59% mutant viral strain in the control group, the difference being statistically non-significant, $p=0.633$.

The data suggests that alcohol has no influence on the viral strain type infection nor on the system "e" seroconversion and the mutant strain dominance that we found fits the current epidemiological profile of the hepatitis B viral infections.

One of the most important indicators of the severity of a chronic hepatopathy is the histological activity index or the necroinflammatory score. (7) We started by assuming that alcohol aggravates the necroinflammatory lesions in patients with chronic viral hepatitis B. (4,7). To this end we analyzed for both the experimental group and the control group the histological activity index, calculated according to the Knodell score. We found a higher necroinflammatory activity in the case group 10.23±1.10 vs. 8.14±1.29 in the control group. The difference is statistically significant, $p<0.0014$. We can confirm the working hypothesis, according to which the alcoholic aggression amplifies the necroinflammatory lesions generated by the virus. The additive effect over the necrotic and inflammatory lesions is probably very small, since in alcoholic hepatopathy those lesions albeit present are not very severe.

A second key parameter used to assess the stage of a hepatopathy is the fibrosis score, which is seen as a result of the necroinflammatory lesions in the liver. (8,9) We found higher values of the fibrosis score 1.97±0,46 for the mixed hepatopathy group and 1,64±0,13 for the viral B hepatitis group. The difference is statistically significant ($t=2.302$, $p=0.0022$). The data reflects on one hand the result of the necroinflammatory lesions, more severe in the case group and leading to fibrosis, and on the other hand the fibrogenic effect that alcohol metabolites possess.

Analyzing the distribution of the fibrosis score by degrees of severity in the 2 groups shows for the cases 0% minimal fibrosis, 31.42% light fibrosis, 40.00% moderate fibrosis and 28.75% severe fibrosis. For the controls we found 4.08% minimal fibrosis, 36.73% light fibrosis, 50.00% moderate fibrosis and 9.18% severe fibrosis. The difference between the two groups is statistically significant ($p=0.0229$). It's easy to see that the higher mean values of the fibrosis score in the mixed hepatopathy group are mainly attributable to a higher percentage of severe fibrosis (28.5% compared to 9.18%), the finding proving once again the severity of the condition.

Macrovacuolar dystrophic lesions are found in 97.14% of the patients with mixed hepatopathy compared to 55.10% in patients with lone chronic viral hepatitis B, the difference between the two lots being statistically significant (Fischer $p<0.0001$). We did find however a high percentage of chronic viral hepatitis B patients having steatosis lesions. That is not an impediment for a good differential diagnosis given the position of the steatosis lesions, mostly pericentrilobular in patients with mixed hepatopathy and mostly periportal or zonal in patients with lone viral hepatitis B. (5,7)

Another lesion being very specific to the alcohol group is the centrilobular vein fibrosis. (5) We found a prevalence of 88.7% in the case group and only 6.12% in the control group. The centrilobular vein fibrosis is rare in the lone viral hepatitis B group (significant difference $p<0.0001$).

We determined the mean values of SGOT (UI/l) in patients with mixed hepatopathy (73.71±11.49) compared to lone hepatitis B (51.09±7.91), $p=0.0035$. The higher values of the SGOT retain their specificity for alcohol induced lesions. (5)

We determined the mean values of SGPT (UI/l) in patients with mixed hepatopathy (93.57±15.77) compared to lone hepatitis B patients (82.43±12.70), p=0,349. The difference is not statistically significant, the increased enzyme values are not indicative of a simultaneous alcohol etiology. (5)

We checked to see whether the GGT (UI/l) levels are relevant to identifying alcohol generated lesions in the mixed group. For the cases we found significantly higher values (72.91±11.46) compared to the controls (47.61±8.78), $p<0.0027$, the enzyme holding its predictive value for alcohol consumption. (5)

The viral load values do not differ significantly in the experimental group ($2.23\pm1.11x10^4$ copies/ml) compared to the control group ($2.05\pm0.66x10^4$ copies/ml), $p=0.45$, so the concurrence of alcohol does not influence viral kinetics.

Regarding the evolution stage of the viral B infection we had 14.28% of the experimental group being in the immune escape phase compared to 21.42% in the control group, $p=0.46$, the difference being not statistically significant.

## DISCUSSIONS

The group composed of patients having mixed hepatopathy (alcoholic plus viral B) has a higher mean age than the hepatitis B group, suggesting an additive effect of alcohol and HBV and not a synergic one. Accumulating additional risk factors with age and an increase in hepatitis B frequency with age may also play a role. (8) The mixed hepatopathy (alcoholic plus viral B) is more often seen in men due to the higher alcohol consumption. (6,8) The alcohol intake doesn't influence the "e" system seroconversion or a specific HB viral sprain, wild or mutant. (8)

The average value of the necroinflammatory score is higher in the mixed hepatopathy group compared to the viral B group, showing that alcohol promotes virus generated lesions. The alcohol by itself rarely produces liver necroinflammation. (5,9) The average value of the fibrosis score is higher in the mixed hepatopathy group compared to the lone chronic viral

hepatitis B, suggesting a cumulated effect – increased necroinflammatory activity plus direct fibrogenesis promoted by alcohol. (1,2,4,5) In the mixed hepatopathy group we found histopathological lesions that are typical for alcohol consumption, such as macrovacuolar dystrophy and perivenular fibrosis, allowing for a simple identification of the lesions generated by alcohol. (5,10,11)

In a similar way, the SGOT and GGT values are higher in the mixed hepatopathy group, allowing us to identify patients with lesions provoked by alcohol. (12) The viral load values don't seem to be influenced by alcohol, nor do the viral B immune escape episodes, the differences between the two groups being statistically insignificant. (13,14,15,16).

## CONCLUSIONS

The mixed hepatopathy (alcohol plus HB) shows in detail all the biological and histological markers of both aggression factors, the effect being an additive one. Viral kinetics, "e" system seroconversion and the viral B immune escape episodes don't seem to be influenced by alcohol. The histological findings of the mixed hepatopathy are much more severe given the cumulating effect of the two factors involved in liver aggression..

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