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HEPATITIS B AND C VIRUS MARKERS AMONG PATIENTS WITH HEPATOSPLENIC MANSONIC SCHISTOSOMIASIS

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SUMMARY

Purpose: To evaluate the frequency and the consequences of the co-infection of hepatitis B and C viruses in patients with hepatosplenic schistosomiasis (HSS).

Methods: B and C serologic markers, exposure to risk factors, biochemical assays, upper gastrointestinal endoscopies, and abdominal ultrasonograms were evaluated in 101 patients with HSS from 1994 to 1997. Whenever possible, PCR was tested and histopathological studies were reviewed.

Results: At least one HBV virus marker was found in 15.8%, and anti-HCV was detected in 12.9% of the subjects. The seropositive subjects tended to be older than the seronegative ones. A history of blood transfusion was significantly related to the presence of anti-HCV. Three (18.75%) out of 16 subjects exposed to B virus were HBsAg positive. Eleven (84.6%) out of thirteen patients who were anti-HCV positive demonstrated viral activity. Patients with ongoing viral infection presented a higher average level of liver aminotransferases, a higher frequency of cell decompensation and a higher rate of chronic hepatitis. Portal hypertension parameters were not influenced by viral exposure.

Conclusions: The rate of hepatitis B and C viruses serologic markers observed in the patients with HSS was higher than the control group. The co-infection was responsible for a higher frequency of cell decompensation.

KEYWORDS: Schistosomiasis; Mansonic Schistosomiasis; Hepatitis; B Virus; C Virus

INTRODUCTION

Schistosomiasis is considered to be the most important helminthic disease of man since it infects about 200 million individuals in about 74 countries in the world[68]. In Brazil, a total of 2.5 million individuals are estimated to be infected by the single autochthonous species, *Schistosoma mansoni*, and 25 million people are at risk to be infected, representing one of our major public health challenges[58].

Subjects are affected in different manners and most infected individuals are asymptomatic carriers of the parasite. The most serious form is the hepatosplenic one, whose major complication is upper digestive hemorrhage secondary to portal hypertension[12,64,65,75]. In pure and uncomplicated cases, hepatocellular function is usually preserved up to the more advanced phases of the disease[79].

Two aspects motivated the study of the role of viral hepatitis in schistosomiasis. The first was the observation that in cases of schistosomiasis that progressed to the decompensated form unusual focal cirrhotic changes could be observed in the liver parenchyma[6,17]. The second was the fact that patients with schistosomiasis show altered behavior when in contact with different pathogens, with possible modifications occurring in the course of the disease in the associated presence of enterobacteria, other helminths and different protozoa[11,18,32,64,77].

Pioneering studies by GUIMARÃES[35] and LYRA *et al.*[50] in the 1970's demonstrated a significantly higher incidence of B virus surface antigen (HBsAg) in individuals with hepatosplenic schistosomiasis (HSS) and suggested that the antigenemia of these patients tended to persist. Anatomopathological studies demonstrated the role of active chronic hepatitis as a decompensating factor in schistosomiasis[7,8,36].

Studies were later conducted in Brazil and in other regions, especially Egypt and other Arab countries, where the prevalence of schistosomiasis and viral hepatitis is very high. The results were not uniform, some of them showing association between B virus and schistosomiasis[2,19,20,37,52,61],

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while others did not demonstrated a higher prevalence[27,28,40,73] or a higher rate of chronification of hepatitis[69].

After characterization of the C virus, many investigators evaluated the role of the major causative agent of "non-A non-B" hepatitis within this context. Several studies conducted in Egypt[1,9,22,28,39,45,46,78] and in Brazil[30,31,48,49,62] demonstrated a higher prevalence of C virus infection in schistosomotic patients and defined its importance in the decompensation of hepatic disease, although other studies did not detect this association[26,38,73].

The mechanisms underlying the greater incidence of viral hepatitis in patients with HSS are probably related to a greater exposure to risk factors to the viruses, and to the possible existence of an immunologic defect in these patients which would make them more susceptible to viral infection, modifying its clinical course. Many studies have been conducted in an attempt to evaluate the aspects of immunity that might be impaired, but the mechanisms are not perfectly understood yet[10,11,15,21,22,28,29,34,36,50,54,55,59,60].

In summary, accumulated evidence suggests the occurrence of a higher prevalence of hepatotropic B and C viruses in schistosomotic patients and that these agents may be important in an eventual unfavorable clinical outcome. However, differences are observed among the various studies depending on the mode of patient selection, and the place and period studied. Thus, the objective of the present study was to evaluate the importance of this association in patients currently seen at a hospital environment.

METHODS

We reviewed the medical records of all patients seen at the Gastroenterology Clinic of Santa Casa de São Paulo, Brazil, from July 1994 to July 1997, with a diagnosis of portal hypertension of presumed schistosomotic etiology. That is an University Hospital located in a non-endemic area for schistosomiasis and that admits patients from all over the country.

A total of 301 patients had been seen in this period and submitted to a protocol applied to all cases of portal hypertension, that consists of testing for its main causes, studies of hepatic function, abdominal ultrasonography and esophagogastroduodenoscopy.

The following patients were excluded: a) patients with other causes of liver disease than schistosomiasis and hepatitis virus B and C; b) patients for whom a definitive diagnosis of schistosomiasis could not be confirmed, and c) patients submitted to multiple blood transfusions for other reasons.

The final series consisted of 101 patients with HSS, 58 females (57.4%) and 43 males (42.6%). Age ranged from 19 to 74 years (mean $\pm$ SD: 40.31 $\pm$ 13.26, and median: 39 years). Seventy-five were Caucasian (75.8%), eight were black (8.1%), and 16 of mixed ethnicity (16.2%), and the color of two patients was not available. The patients were from Northeastern states and from Minas Gerais.

The control group consisted of donors registered at the blood bank of the same hospital. The mean value of the positive results for HBsAg, of the antibody against B virus core protein (anti-HBc) and of the antibody against C virus (anti-HCV) was calculated for 29,406 blood donors from January 1996 to August 1997.

The status of each patient with respect to infection with B and C virus was determined by serologic methods and by the search for deoxyribonucleic acid of B (HBV-DNA) and ribonucleic acid of C virus (HCV-RNA) by the polymerase chain reaction (PCR), whenever possible. These results, taken together with the analysis of hepatic histology, permitted grouping the patients as follows:

Group I: presence of any marker of B virus
- **I.a.** HBsAg positive.
- **I.b.** HBsAg negative.

Group II: Anti-HCV positive.
- **II.a.** with evidence of active infection: PCR positive and/or suggestive histopathologic pattern
- **II.b.** no evidence of active infection

Group III: Absence of markers for hepatitis B and C virus.

Patients were considered to be decompensated when they presented one or more of the following disorders[66]: ascites, jaundice, coagulopathy (prothrombin activity < 60%), hypoalbuminemia (albumin < 3.0 g/dl), or encephalopathy.

Data concerning medical history and physical examination were extracted from the medical records. The search for *Schistosoma mansoni* eggs in feces was performed by the method of Kato-Katz (1972) or by rectal biopsy. Serologic tests for schistosomiasis were performed using adult worm antigens[43] with three methods being applied to each patient (enzyme immunoassay (EIA), indirect immunofluorescence reaction, and hemagglutination reaction). A result was considered to be positive when the data of the three tests were consistent. The microparticle enzyme immunoassay technique was used for the detection of serologic markers of B virus (Abbott). Anti-HCV were detected by 2nd or 3rd generation EIA techniques using commercial kits. The HBV-DNA was detected by the PCR according to a previously described technique[44] and the RNA-HCV was detected with the Amplicor® kit (Roche).

To exclude other causes of liver disease, a laboratory screening was performed for the following diseases (data not shown): hemochromatosis, Wilson's disease, autoimmune hepatitis, alpha-1 antitrypsin deficiency, and to exclude hepatocarcinoma alpha-fetoprotein and ultrasonography were used. For the evaluation of the extent of hepatocellular damage and of hepatic synthesis function we analyzed aminotransferases, albumin, and prothrombin activity. Ultrasonography and esophagogastroduodenoscopy were performed according to the routine of the respective services.

For the purposes of the present study, the anatomopathologic examination was reviewed by the same pathologist. Cases of viral hepatitis were classified according to the traditional nomenclature[42].

Data were analyzed statistically by the chi-square test and the exact Fisher test for comparison of proportions, by the Student t-test and by analysis of variance for comparison of the means, and by the

nonparametric Kruskal-Wallis test for quantitative variables with no normal distribution or homogeneity of variance. The level of significance was set at 5% and the calculations were performed using the Epi-info software, version 6.04 B.

RESULTS

Seventeen patients (15.8%) were positive to some marker of B virus and represented Group I. Thirteen patients (12.9%) had antibodies against C virus and represented Group II. No marker was detected in 72 patients (71.3%).

Table 1 shows that the frequencies of anti-HBc and of anti-HCV differed significantly between individuals with HSS and controls

There was no significant difference in patient sex or color according to the presence of viral markers. With respect to age distribution, Table 2 shows that patients with B virus markers (Group I) or C virus (Group II) markers were older than patients with pure schistosomiasis (Group III).

With respect to the presence of risk factors for hepatitis B and C, Table 3 shows that the frequency of a history of blood transfusion was higher in Group II. The analysis of other risk factors showed no significant differences.

Among B marker carriers (Group I), three patients were positive for HBsAg and were assigned to Group Ia. One case tested positive for anti-e antibodies, negative for HBV-DNA and a liver biopsy was inconclusive due to insufficient material. The second patient also tested positive for anti-e antibodies. He died and autopsy revealed the presence of cirrhosis. In the third patient, who was not tested for viral replication markers, hepatic histology showed active hepatitis.

Among anti-HCV positive patients, 11 patients showed evidence of viral activity (demonstrated by the positivity in PCR in four cases, by hepatic histology in five, and by both parameters in two) and formed subgroup IIa. Subgroup IIb consisted of two patients, one with PCR negative and with no material available for hepatic histology, and the other with hepatic histology presenting no changes suggestive of viral hepatitis.

The analysis of some parameters concerning portal hypertension showed a significantly greater mean spleen enlargement in Group III. Other parameters evaluated, such as caliber of the portal vein, frequency of patients submitted to surgery and frequency of patients with esophagogastric varices and/or hypertensive gastropathies, did not show significant differences.

The results listed in Table 4 demonstrate that there was a significant difference between groups in terms of mean aspartate aminotransferase (AST) levels, with a *p* value of 0.06 for mean alanine aminotransferase (ALT) levels. These differences were the result of greater alterations in Group II. In subgroup Ia there were also important alterations in AST levels.

According to the criteria mentioned in Methods, the patients were classified according to the presence or absence of hepatocellular decompensation. Table 5 demonstrates that this decompensation was observed more frequently in Group II patients. It can be seen that the high percentage for Group II was due to subgroup IIa, and that all patients in Group Ia had the decompensated form.

Table 1
Proportion of viral markers in patients with HSS studied from July 1994 to July 1997 and in blood donors, SCSP

	HSS		Donors		
Marker	***Freq.***	***%***	***Freq.***	***%***	
HBsAg	3	3.0	248	0.84	$p = 0.055$
Anti-HBc	16	15.8	1843	6.20	$p < 0.001$
Anti-HCV	13	12.9	394	1.34	$p < 0.001$
Sample	101		29406		

HSS: hepatosplenic schistosomiasis; SCSP: Santa Casa de São Paulo

Table 2
Range, mean and standard deviation for age in years in HSS studied patients between July 94/July 97, SCSP

Group	***Range***	***Mean***	***Standard deviation***
I (HBV)	34 - 74	54.31	10.21
II (HCV)	38 - 72	51.31	11.35
III	19 - 65	35.21	10.55
Total	19 - 74	40.31	13.26

$F = 29.31$; $p < 0.001$

Table 3
Proportion of patients with a history of blood transfusion in HSS studied patients between July 94/July 97, SCSP

Group	***Freq.***	***%***
I (HBV)	9 (16)	56.3
II (HCV)	10 (13)	76.9
III[1]	28 (70)	40.0
Total	47 (99)	47.5

$X^2 = 6.58$, 2 g.l.; $p < 0.05$; The numbers in parenthesis indicate the total number of patients in each group; [1] Information not available for two cases in Group III.

Although Group III patients presented a lower proportion of decompensation compared to subgroups Ia and IIa, decompensation was present in a considerable number of patients in this group (37.5%). No current viral infection was detected in 70% of the decompensated cases (groups Ib and III). We then analyzed the patients in subgroups Ia, IIa and in group III according to each criterion. The results are shown in Table 6.

Material for analysis of hepatic histology was available for 53 patients (52.2%), 11 of them belonging to Group I, eight to Group II, and 34 to Group III. Seven out of ten patients whose histologic pattern revealed

Table 4
Mean and standard deviations of AST and ALT levels in HSS studied patients between July 94/July 97, SCSP

Group	*Freq.*	*AST (U/l)* $\bar{x}$ *	s	*ALT (U/l)* $\bar{x}$ **	s
I (HBV)	15	42	22	28	16
I a	2	68	41	42	19
I b	13	38	17	26	15
II (HCV)	13	76	58	70	93
II a	11	80	63	73	102
II b	2	53	13	53	12
III	72	39	17	35	21
Total	100[1]	44	29	39	39

[1] Information not available for a patient in group I a; * $p < 0.05$ (comparison of Groups I, II and III); ** $p = 0.06$ (comparison of Groups I, II and III); $\bar{x}$ = mean; ***s*** = standard deviation

Table 5
Proportion of hepatic decompensation in HSS studied patients between July 94/July 97, SCSP

Group	*Decompensation Freq.*	*%*
I (HBV)	4 (16)	25.0
I a	3 (3)	100.0
I b	1 (13)	7.7
II (HCV)	9 (13)	69.2
II a	9 (11)	81.8
II b	- (2)	-
III	27 (72)	37.5
Total	40 (101)	39.6

$X^2 = 6.38$, 2 g.l; $p < 0.05$.

Table 6
Distribution according to the criteria of hepatic decompensation in two groups of HSS patients between July 94/July 97, SCSP

Group	*II a (n = 11)* *Freq.*	*%*	*III (n = 72)*[1] *Freq.*	*%*	*p*
Coagulopathy	8	72.3	16	22.2	0.002
Ascites	4	36.3	9	12.8	0.06
Alb<3.0 g/dl	1	9.1	4	5.6	0.51
Jaundice	1	9.1	3	4.2	0.44
Encephalopathy	1	9.1	-	-	-

chronic hepatitis with or without cirrhosis had hepatitis C. The other three presented B virus markers, two of them being HBsAg positive and one whose serologic results suggested immunity. The pattern observed in this patient was cirrhotic.

DISCUSSION

The samples studied consisted exclusively of individuals from other States. The predominance of females was probably related to the exclusion of alcoholics, who are more frequent males. In mansonic schistosomiasis, sex distribution is usually uniform[13].

With respect to color distribution, there was a relatively high frequency of Caucasian individuals although they were from locations where this race is less prevalent. According to data of the 1991 Census of the Brazilian Institute of Geography and Statistics[41], the mean percentage of blacks and individuals of mixed ethnicity in the five states studied here is 63.6%. In the group of patients studied, this percentage was 24.3%. This feature may reflect the greater resistance of black patients to the development of the severe forms of the disease, as observed by some investigators[13,14].

The presence of serologic markers of B virus (15.8%), of HBsAg (3%) and of anti-HCV (12.9%) among patients with HSS was higher than that observed among blood donors and among historical controls[62,71].

For comparative purposes with data in the literature, it is important to point out that patients were selected in a hospital environment, so that the data do not reflect the situation occurring in an endemic area[47,70]. The laboratory tests used should also be considered[50,51]. More recent studies have used more sensitive and specific techniques for the detection of viral markers.

With respect to B virus markers, even though a higher frequency was detected in patients with HSS than in controls, a tendency to a reduction of this difference can be observed when our data are compared to those obtained in previous studies conducted in Brazil. In the early 1980's, GUIMARÃES *et al.*[36] and LYRA[51] reported positivity of 22.5% and 23.3%, respectively, for HBsAg in patients with HSS. COELHO *et al.*[19], in a 1985 study of 19 patients with chronic hepatitis associated with HSS, detected an equal number of cases whose etiology was B virus and non-A non-B virus, emphasizing the declining relative causal importance of B virus in these cases. In more recent studies, PEREIRA *et al.*[61] observed in 1994 that 11.8% of patients with HSS, compensated or not, carried HBsAg and that 38.5% carried any marker of B virus. LINS[49] found a difference in the frequency of HBsAg between schistosomotic patients (4.1%) and controls, although without statistical significance.

This tendency probably reflects a period during which the probability of contamination of schistosomotic patients with B virus by blood transfusion has become progressively lower, both because of the screening adopted by blood banks since the early 1970's and of the better treatment received by these patients for portal hypertension, with a reduction in hemorrhagic episodes and in the need for hospitalization and blood transfusions[65,72,76].

Serologic tests for the detection of anti-HCV were set up as part of the routine of our blood banks in the early 1990's. Thus, the population of schistosomotic patients investigated during this period barely reflects the benefits of this screening. However, even before these tests were set up, a decline in post-transfusional hepatitis could be observed due to the additional screening measures adopted by blood banks[3,53]. In Brazil, the

frequency of anti-HCV detected by EIA in patients with HSS has been consistently high[30,31,48,49,62], ranging from 12.4%[49] to 26.7%[62] .

The observation that more advanced age is associated with a higher frequency of B and C viruses markers reflects the cumulative risk of exposure to the viruses.

Many investigators believe that the higher frequency of hepatitis virus markers in HSS may be related to the therapeutic measures applied to this group, since these patients are frequently submitted to surgery and/or present digestive bleeding when they receive blood transfusions[8,37,51,72,74]. After contact with the virus, a component of hepatocellular aggression would be progressively added to the schistosomotic lesions, until then of a preponderantly vascular and mesenchymal nature[8].

Reuse of the needle for parenteral treatment of schistosomiasis (hycanthone) was a common practice in Egypt up to the beginning of the 1980's, and probably contributed to the transmission of B and C viruses[22,26,28,39]. In Brazil, parenteral treatment of schistosomiasis was discontinued at the beginning of the 1970's.

An aspect to be considered is the time of exposure to each pathogen. In regions where the prevalence of the virus is very high, exposure may occur before contact with *Schistosoma*, which is unlikely to influence the course of hepatitis[23]. The disease is presumably more severe among those individuals with viral infection superimposed on schistosomotic disease. In Brazil, exposure to the virus probably occurs after exposure to *Schistosoma mansoni*, which usually occurs in early childhood in endemic areas[75]. The data in Table 2 support this idea.

With respect to the exposure to risk factors, we observed a significant difference in the history of blood transfusion, in terms of C virus as compared to the other groups. The frequency of exposure to other risk factors was not marked in the present study.

Another aspect to be discussed is the possible occurrence of "potentiation" of viral infections[18,22], causing an altered clinical course of hepatitis in patients with HSS[33,51].

In the present study, three of 16 patients with B virus markers (18.75%) were HBsAg positive (subgroup Ia). This ratio is therefore slightly higher than the estimate for the adult population, i.e., about 5 to 10% [3]. All subjects presented clinical and/or biochemical signs of hepatocellular decompensation, and chronic hepatitis was demonstrated histopathologically in two cases. Among the 13 patients who were anti-HCV positive, 11 (84.6%) presented evidence of active viral infection as shown by positivity of the PCR and/or by histopathological examination showing chronic hepatitis or cirrhosis. A characteristic of this virus is its high potential for progression to chronicity, with viral infection remaining active in up to 85% of patients[56]. Thus, our data suggest, although they do not confirm precisely, that there is difficulty in B or C virus clearance in patients with HSS.

Comparison of parameters concerning portal hypertension between groups showed significance only in terms of spleen size, which was larger in Group III patients. This result contradicts the hypothesis raised by GHAFFAR *et al.*[33] who suggested that splenomegaly may develop during B virus infection in patients with uncomplicated schistosomiasis, an alternative hypothesis to the one more accepted in the literature that patients with HSS may be more susceptible to viral infection. With respect to the other parameters evaluated, apparently there was no higher degree of portal hypertension in cases of associated viral hepatitis. This suggests that the portal hypertension in the studied group must be mainly due to schistosomiasis rather than to viral infection.

We observed a significant alteration in hepatic aminotransferase levels, especially AST, in patients anti-HCV or HBsAg positive (Table 4), in agreement with several studies[37,51,52,61,62].

Table 5 shows that decompensation was more frequent in patients with active viral infection (subgroup "a"). However, only 30% of all decompensated patients belonged to these groups and decompensation occurred in 37.5% of Group III patients. In the group of patients with decompensated HSS studied by PEREIRA *et al.*[62] from March 1990 to April 1993, 70% of patients had active B or C virus infection.

These data suggest that the presence of viral infection could be an important factor in the decompensation of patients with HSS, although decompensation can occur in the absence of this factor in a considerable number of cases. Thus, an attempt was made to determine on the basis of what criteria these patients were considered to be decompensated. Analysis of Table 6, which compares the frequency of decompensation among patients with ongoing C hepatitis associated to schistosomiasis to those with pure schistosomiasis shows that it was more frequent in individuals with active viral infection on the basis of all criteria adopted, but that it reached statistical significance only in terms of coagulopathy. Among patients with pure schistosomiasis (Group III), cases of decompensation occurred on the basis of all criteria, except encephalopathy.

In spite of a significantly smaller occurrence of coagulopathy in patients with pure HSS, it occurred in 22.2% of these patients. Several disorders of coagulation can occur in this disease due to reduced production, increased consumption and impaired hepatic clearance of both coagulant and anticoagulant proteins, with the possible occurrence of chronic consumption coagulopathy and hyperfibrinolyis among other alterations[4,5,16,25,57].

The occurrence of ascites in 12.8% of patients with pure HSS agrees with the literature and represents the major clinical sign of decompensation[63,66]. Hypoalbuminemia may be secondary to extrahepatic factors such as deficiency states and multiple helminth infections, frequently present in these patients, and to proteinuria due to glomerular involvement[67]. On the other hand, the presence of encephalopathy should not be expected since these patients have been shown to have normal ammonia tolerance[80]. Jaundice rarely occurs and its presence should raise the suspicion of viral hepatitis[66].

Thus, we believe that the classification of HSS into compensated and decompensated forms deserves a more up-to-date approach with emphasis on the degree of decompensation, for a better sensitivity with respect to the presence of associated morbid conditions. Indeed, different intermediate degrees can occur among compensated or severely decompensated individuals[66], and some alterations of hepatic function, such as coagulopathy, may occur as an early event in pure schistosomiasis[16].

These data of hepatic histology suggest that the presence of a pattern of chronic hepatitis may be relatively specific for the presence of hepatotropic viruses, as suggested by early observations[6-8,24].

Finally, with respect to an overall evaluation of the role of the association of hepatotropic viruses with schistosomiasis mansoni, we conclude that the presence of markers may be mainly due to the greater exposure of these individuals to risk factors, with this association tending to be less and less observed with a better control of these factors. However, it is possible that these patients, once exposed to the virus, tend to present difficulties in its clearance. This factor may have contributed to the persistence of a discrete increase in the frequency of the virus in this group of patients, associated with the deterioration of hepatocellular function and histological signs of chronic hepatitis.

RESUMO

Marcadores para vírus da hepatite B e C em pacientes com esquistossomose mansônica hepatoesplênica

Objetivo: Avaliar a freqüência e repercussões da co-infecção com os vírus B e C da hepatite em pacientes com esquistossomose hépato-esplênica (EHE)

Métodos: Marcadores sorológicos dos vírus B e C, exposição aos fatores de risco, determinações bioquímicas, endoscopia digestiva alta e ultrassonografia abdominal foram avaliados em 101 portadores de EHE entre 1994 e 1997. A PCR e a análise dos aspectos histopatológicos foram realizadas quando possível.

Resultados: Pelo menos um marcador sorológico do vírus B foi identificado em 15,8% e o anti-HCV em 12,9% dos pacientes. A média de idade foi significativamente superior nos soropositivos. O antecedente de tranfusão sangüínea correlacionou-se significativamente com a presença de anti-HCV. A relação entre os pacientes HBsAg positivos e o total de indivíduos expostos ao vírus B foi de 18,75%. Dentre os anti-HCV positivos, 84,6% apresentaram indícios de infecção viral em atividade. Os pacientes com infecção viral atual apresentaram maior média das aminotransferases, maior freqüência de descompensação hépato-celular e de hepatite crônica. Não se observaram alterações nos parâmetros relativos à hipertensão portal.

Conclusões: A freqüência de marcadores sorológicos para os vírus B e C nos portadores de EHE foi significativamente superior à do grupo controle. A co-infecção foi responsável por uma maior freqüência de descompensação hépato-celular.

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