Article/Artigo

Liver fibrosis progression in HIV/hepatitis C virus coinfected patients with normal aminotransferases levels

Progressão da fibrose hepática em portadores de coinfecção HIV/vírus da hepatite C com níveis de aminotransferases normais

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ABSTRACT

Introduction: Approximately 30% of hepatitis C virus (HCV) monoinfected patients present persistently normal alanine aminotransferase (ALT) levels. Most of these patients have a slow progression of liver fibrosis. Studies have demonstrated the rate of liver fibrosis progression in hepatitis C virus-human immunodeficiency virus (HCV-HIV) coinfected patients is faster than in patients infected only by HCV. Few studies have evaluated the histological features of chronic hepatitis C in HIV-infected patients with normal ALT levels. **Methods**: HCV-HIV coinfected patients (HCV-RNA and anti-HIV positive) with known time of HCV infection (intravenous drugs users) were selected. Patients with hepatitis B surface antigen (HBsAg) positive or hepatitis C treatment before liver biopsy were excluded. Patients were considered to have a normal ALT levels if they had at least 3 normal determinations in the previous 6 months prior to liver biopsy. All patients were submitted to liver biopsy and METAVIR scale was used. **Results:** Of 50 studied patients 40 (80%) were males. All patients were treated with antiretroviral therapy. The ALT levels were normal in 13 (26%) patients. HCV-HIV co-infected patients with normal ALT levels had presented means of the liver fibrosis stages (0.77±0.44 *versus* 1.86±1.38; p<0.001) periportal inflammatory activity (0.62±0.77 versus 2.24±1.35; p<0.001) and liver fibrosis progression rate (0.058±0.043 fibrosis unit/year *versus* 0.118±0.102 fibrosis unit/year) significantly lower as compared to those with elevated ALT. **Conclusions:** HCV-HIV coinfected patients with persistently normal ALTs showed slower progression of liver fibrosis. In these patients the development of liver cirrhosis is improbable.

Keywords: Liver cirrhosis. Hepatitis C. HIV. Aminotransferase.

RESUMO

Introdução: Aproximadamente, 30% dos portadores de hepatite crônica C apresentam níveis de aminotransferases persistentemente normais (APNL). A maioria destes pacientes tem lenta progressão da fibrose hepática. Em portadores de coinfecção VHC-HIV, estudos têm demonstrado que a progressão da fibrose hepática é mais rápida que a observada em indivíduos infectados somente pelo VHC. Há poucos estudos que verificaram as características histológicas da hepatite crônica C em pacientes coinfectados pelo HIV APNL. **Métodos:** Portadores de coinfecção VHC-HIV (HCV-RNA e anti-HIV positivos) com tempo de infecção pelo VHC conhecido (uso de drogas intravenosas) foram selecionados. Aqueles com *hepatitis B surface antigen* (HbsAg) positivo ou que tenham sido submetidos à terapia antiviral para hepatite C antes da biópsia hepática foram excluídos. Pacientes com pelo menos 3 determinações normais da ALT nos últimos 6 meses antes da biópsia hepática foram considerados como tendo APNL. Todos foram submetidos a biópsia hepática que foi classificada de acordo com a escala METAVIR. **Resultados:** Foram incluídos 50 pacientes, 40 (80%) homens. Todos receberam terapia antirretroviral. Os níveis de ALT foram persistentemente normais em 13 (26%) pacientes. Pacientes coinfectados com APNL apresentaram menor média dos estágiosde fibrose hepática (0,77±0,44 *versus* 1,86±1,38; p<0,001), dos índices de atividade inflamatória periportal (0,62±0,77 *versus* 2,24±1,35; p<0,001) e progressão mais lenta da fibrose hepática (0,058±0,043 unidades de fibrose /ano *versus* 0,118±0,102 unidades de fibrose/ano) quando comparados àqueles com aminotransferases elevadas. **Conclusões:** Portadores de coinfecção VHC-HIV com APNL apresentam progressão mais lenta da fibrose hepática. Nesses pacientes o desenvolvimento de cirrose hepática é improvável.

Palavras-chaves: Cirrose hepática. Hepatite C. HIV. Aminotransferases.

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INTRODUCTION

Due to shared risk factors for transmission of coinfection with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) it is a very common event. It is estimated that around 30% of HIV-infected patients are coinfected with HCV in the United States and Europe[1-7]. The mode of HIV acquisition is directly associated with prevalence rates of HCV co-infection. Thus, the prevalence of HCV among men who have sex with men is approximately 10%, while 70-90% of the intravenous drugs users (IDU) are HCV co-infected[1,8,9].

Liver disease caused by HCV is now the leading cause of morbidity and mortality among HIV-infected patients in the developed world where classic severe immunodeficiency opportunistic infections have considerably declined as a result of the widespread use of potent antiretroviral therapy[10-15].

Several studies have demonstrated the deleterious HIV immunodeficiency action on the natural history of chronic hepatitis C. The rate of liver fibrosis progression in HCV-HIV coinfected patients is about 1.5 to 2 times faster than in patients infected only by HCV[16-20]. However, most of the studies were carried out during the pre-highly active antiretroviral therapy (HAART) era and only HCV-HIV coinfected patients with elevated aminotransferases levels were included, which may have overestimated the severity of the HCV induced liver disease.

The real effect of HAART on the natural history of chronic hepatitis C in HIV infected patients is still unclear. Two studies reported that HCV-HIV coinfected patients submitted to HAART based on the use of protease inhibitors presented slower liver fibrosis progression[21,22]. Another study published by Qurish et al. found that HAART reduced liver related mortality in HCV-HIV coinfected patients[23]. On the other hand, Zylberberg et al described that the immunologic reconstitution after HAART

accelerated progression of chronic hepatitis C to more advanced liver fibrosis stages[24] and Antonello et al reported that coinfected patients showed a higher aspartate aminotransferase to platelet ratio index (APRI), a noninvasive liver fibrosis marker, after six months of HAART when compared with hepatitis C monoinfected patients[25].

Approximately 30% of chronic hepatitis C carriers present persistently normal alanine aminotransferase (ALT) levels. Most of these patients show mild histological lesions and have slow liver fibrosis progression[26,27]. Prospective studies and outcome modeling projections suggest that the risk of liver disease progression towards severe fibrosis/cirrhosis is minimal at 10-15 years in hepatitis C virus carriers with persistently normal ALT[28].

In the world, few studies have evaluated the behavior of chronic hepatitis C in HIV-infected patients with normal aminotransferases levels[29-31]. In HCV-HIV coinfected Brazilian patients, the prevalence of individuals with normal aminotransferases levels, the rate of liver fibrosis progression and their histological characteristics, remain to be studied.

METHODS

From June 2001 to June 2004, there were, HCV-HIV coinfected patients followed in Federal University of São Paulo, Brazil, based on serum antibody detection with a third generation enzyme-linked immunosorbent assay. Serum HCV-RNA was detected by qualitative polimerase chain reaction (PCR-Amplicor; Roche Diagnostic Systems). Only patients with known HCV infection duration were selected. The HCV infection onset was considered as the first year of intravenous drugs usage, or transfusion. Exclusion criteria: presence of hepatitis B surface antigen (HBsAg) or hepatitis C treatment before liver biopsy. Patients were considered to have normal ALT if they had at least 3 normal determinations (lower than the upper limit of normal) in the previous 6 months prior to liver biopsy were included in Group 1 (G1). Patients with altered aminotransferases levels were included in Group 2 (G2). All patients were submitted to liver biopsy independent of ALT levels. Using METAVIR classification, a single experienced pathologist performed the histological evaluation. The fibrosis progression rate (FPR) was defined as the ratio between the fibrosis stage and HCV infection duration (fibrosis units/year). To calculate the time required until the development of cirrhosis was divided 4 (F4 = cirrhosis) by the fibrosis progression rate in fibrosis units/year. Advanced liver fibrosis and intense inflammatory activity was considered when they are ≥ 2.

Statistical analyses

Quantitative variables were expressed as average ± standard deviation (SD) and were compared using the Student´s *t*-test. Percentages were compared using χ^2 test and Fisher´s exact test when appropriate. A difference was considered significant if the P-value was less than 0.05. The Statistical Package for the Social Sciences (SPSS) software package version 10 (SPSS Inc., Chicago, IL) was used.

Ethical considerations

The study was approved by the Research Ethics Committee of the São Paulo Hospital of the Federal University of São Paulo.

RESULTS

Seventy-nine patients with positive antibody anti-HCV and HCV infection with known duration were selected. Three of these were excluded by presenting the HBsAg, four due to the absence of HCV-RNA, and 22 patients for loss of the pursuing or refusing the liver biopsy. Then, 50 patients were included. The average age at liver biopsy was 38±6.6 years and 40 (80%) were males. The use of intravenous drugs was considered the virus acquisition mode in 43 (86%) patients. All patients were treated with antiretroviral therapy and 82% of them used HAART (**Table 1**). The cluster of differentiation (CD4) cell count was above 200 cells/mm^3 in 84% of patients and the HIV viral load was less than 400 copies/mm^3 in 48% of the sample (**Table 2**). The ALT levels were considered normal in 13 (26%) patients. Advanced liver fibrosis (fibrosis stage ≥ 2) and inflammatory activity ≥ 2 were identified in 36% and 54% of the sample, respectively (**Table 3**).

Regarding ALT levels, both of groups showed similar demographic characteristics and alcohol consumption (**Table 1**). In addition, the immunological parameters related to HIV infection and genotype distribution were not different between two groups (**Table 2**).

With respect to histological findings, the HCV-HIV co-infected patients with normal ALT levels had an average of the liver fibrosis stages (0.77±0.44 *versus* 1.86±1.38;

TABLE 1 - Comparative analysis of clinical characteristics between patients with normal and altered aminotransferases levels (n = 50).

	All (n = 50)		Normal ALT (n = 13)		Altered ALT (n = 37)		
Variables	**n**	**%**	**n**	**%**	**n**	**%**	**P**
Men	40	80.0	11	85.0	29	78.0	NS
Age at biopsy - years (mean ± SD)	38.5±6.6		38±7.8		39±6.2		NS
Age at HCV infection - years (mean ± SD)	21.5±7.9		22±8.4		21±7.8		NS
HCV infection duration - years (mean ± SD)	17.1±5.5		16±5.5		17±5.5		NS
Alcohol consumption > 50g/day	25	50.0	6	46.0	19	51.0	NS
Drug intravenous user	43	86.0	10	77.0	33	89.0	NS
HAART	41	82.0	11	85.0	30	81.0	NS
PI use	23	46.0	6	46.0	17	46.0	NS

ALT: alanine aminotransferase; **SD:** standard deviation; **HCV:** hepatitis C virus; **HAART:** highly active anti-retroviral therapy; **PI:** protease inhibitor; **NS:** not significant.

TABLE 2 - Comparative analysis of biological parameters between patients with normal and altered aminotransferases levels (n = 50).

	All (n = 50)		Normal ALT (n = 13)		Altered ALT (n = 37)		
Variables	**n**	**%**	**n**	**%**	**n**	**%**	**P**
CD4 count - cells/mm^3 (mean ±SD)	424.3±234.4		472±332		407±191		NS
HIV viral load - copies/mm^3 (mean ±SD)	13.451±28.452		14.016±17.808		12.847±31.556		NS
CD4 count > 200cells/mm^3	42	84.0	11	85.0	31	84.0	NS
HIV viral load < 400/copies	24	48.0	5	38.0	19	51.0	NS
HCV genotype* non-1	28/43	65.0	10	77.0	18	48.0	0.11

ALT: alanine aminotransferase; **CD4:** cluster of differentation; **SD:** standard deviation; **HIV:** human immunodeficiency virus; **HCV:** hepatitis C virus; *n=43; **NS:** not significant.

p<0.001) and periportal inflammatory activity (0.62±0.77 *versus* 2.24±1.35; p<0.001) significantly lower when compared to HCV-HIV coinfected patients with altered aminotransferases levels. None of the patients with normal ALT levels had advanced liver fibrosis stages. Only two (15%) patients of group 1 had severe inflammatory activity. Furthermore, HCV-HIV co-infected patients with normal aminotransferases levels showed significantly lower liver fibrosis progression rates (0.058±0.043 fibrosis unit (FU)/year *versus* 0.118±0.102 FU/year) when compared to patients from group 2 **(Table 3)**. The interval between HCV infection and development of liver cirrhosis (F4), assuming that the fibrosis progression rate is linear, it was 69 (F4/0.058) and 34 years (F4/0.118) for groups 1 e 2, respectively **(Figure 1)**.

TABLE 3 - Comparative analysis of histological findings between patients with normal and altered aminotransferases levels (n = 50).

Variables	Normal ALT (n=13)		Elevated ALT (n=37)		P
	n	%	n	%	
Liver fibrosis stage (mean ± SD)	0.77±0.44		1.86±1.38		< 0.0001
Inflammatory activity (mean ± SD)	0.62±0.77		2.24±1.35		< 0.0001
FPR (mean ± SD)	0.058±0.043		0.118±0.102		0.006
Fibrosis stage ≥ 2 (n/%)	0	0.0	18	49.0	0.002
Inflammatory activity ≥ 2 (n/%)	2	15.0	25	68.0	< 0.0001

ALT: alanine aminotransferase; **SD:** standard deviation; **FPR:** fibrosis progression rate in units fibrosis/year.

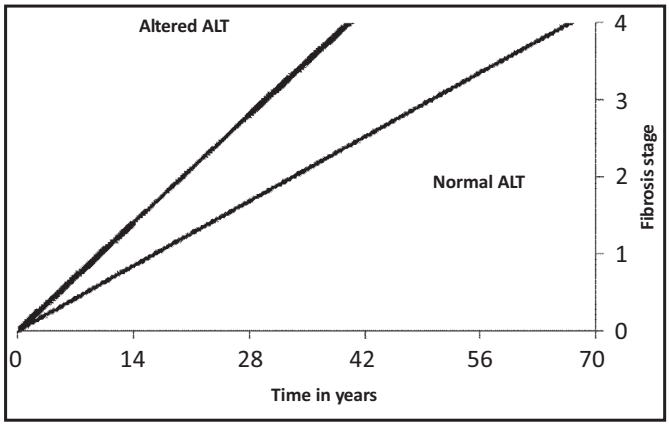

FIGURE 1 - Estimated time to the development of liver cirrhosis according to the ALT levels (n = 50).
ALT: alanine aminotransferase.

DISCUSSION

In healthy patients the normal range for serum ALT level was set in the 1955 by Karmen[32] and has changed little since then. Current upper limit of normality (ULN) were set, on average, from 30 to 50U/L. This was recently challenged by a research group, who claimed that the true normal values are significantly lower. Prati et al suggested that the updated upper limit of normality of alanine aminotransferase should be 30U/L for males and 19U/L for females in subjects with the lowest risk for liver disease[33].

In chronic hepatitis C patients the definition of persistently normal ALT activity (PNALT) no has consensus. Guidelines from the American Association for the Study of Liver Disease suggest that at least two ALT measurements within the normal range taken over at least 6 months can define those with PNALT[34]. Fonquernie et al. considered PNALT coinfected patients with normal ALT levels documented by repeated testing (at least three values per year) over a 3-year period[29]. A French study by Bani-Sadr et al, coinfected patients with persistently normal ALT levels were defined as those having three consecutive persistently normal ALT levels over a 6-month period[30] the same criteria adopted in this study.

Although chronic HCV infection is associated with elevation of ALT activity in most patients, approximately 25% presented serum ALT activity that is persistently within the normal range[35]. Fonquernie et al. reported among 155 HCV-HIV coinfected patients, 39 (28.5%) had persistently normal ALT levels[29]. In study involving 381 HCV-HIV coinfected patients, Bani-Sadr et al. identified 36 (9.4%) subjects with persistently normal ALT values[30]. Sanchez-Conde et al. reported 24/256 (9.4%) HIV-HCV coinfected patients with persistently normal ALT levels[31]. In the present study, we found 13/50 (26%) coinfected patients on HAART with persistently normal aminotransferases levels. The variable criteria of PNALT used among several studies may explain the different prevalence rates observed.

In chronic hepatitis C, comparisons between normal and elevated ALT patients have not identified clear differences that could be used as ALT level predictive factors. In this study, there was a tendency to genotype non-1 in patients with altered aminotransferases levels (9% *versus* 44%; p=0.06). In the Sanchez-Conde study, patients infected with HCV genotype 3 were significantly more common between patients with altered ALT levels than in patients with persistently normal ALT levels[31]. In the Bani-Sadr study, a lower mean METAVIR inflammation score, the absence of steatosis and HCV genotype 4 were associated with persistently normal ALT levels[30]. In the Fonquernie study, three factors associated with persistently normal ALT levels were identified, namely: HBsAg negativity, HCV genotype 4 and female sex[29].

The natural history of chronic hepatitis C is variable. Since most patients with HCV-related chronic hepatitis do not develop cirrhosis, it is logical to infer that host-related and virus-related factors must play a role in the progression to cirrhosis. Liver disease progression takes place over several decades, and is accelerated in the presence of cofactors such as alcohol consumption, insulin resistance, steatosis, older age of acquisition and HIV coinfection. Definition of histological features and liver disease progression in individuals with HCV and normal ALT is complicated because the absence of a gold standard definition for PNALT. Nevertheless, it is generally accepted that individuals with PNALT have milder liver histology when compared to patients with elevated aminotransferases levels[36,37].

Most studies have shown that in HCV-HIV coinfected patients liver fibrosis progression is faster than in HCV monoinfected patients[16-20]. There are few studies that analyze liver histology in HIV-HCV coinfected patients with PNALT. In this study, individuals with normal aminotransferase levels showed mild histological lesions and slower liver fibrosis progression. In the Bani-Sadr study, none of the 36 patients with PNALT had cirrhosis[30]. In coinfected patients with normal aminotransferases levels Fonquernie et al demonstrated a significantly lower fibrosis score and fibrosis progression rate[29]. In this study, factors known to be related to the progression of chronic hepatitis C in monoinfected patients such gender, alcohol consumption and age at time of infection were similar in both groups.

The variables related to cirrhosis development in coinfected patients in according with Benhamou study were similar too[17]. The slower progression of liver fibrosis in coinfected patients with persistently normal ALT levels could be related, in part, to a lower frequency of steatosis in according to the Bani-Sadr study[30]. In the present study, this histological feature was not analyzed. In this study only two patients (15%) in PNALT group showed significant inflammatory activity which may in part at least explain the slower liver fibrosis progression rate in these patients. Potential limitations that could affect this study's results is that the number of PNALT patients was not high and the absence of a uniform definition for PNALT makes comparisons across different studies difficult.

In conclusion, this study could demonstrate that HCV-HIV coinfected patients with persistently normal aminotransferases exposed to antiretroviral therapy would show mild histological lesions. In these patients liver cirrhosis development is improbable.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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