Arab Journal of Gastroenterology 16 (2015) 50–53

Contents lists available at ScienceDirect

Arab Journal of Gastroenterology

journal homepage: www.elsevier.com/locate/ajg

Original Article

Relation of ALT and AST levels to the histopathological changes in liver biopsies of patients with chronic hepatitis C genotype 4

Hany Khattab [a], Ahmed Fouad [b], Maya Hamza [a], Mohammad A. Mohey [b,*], Wafaa El-Akel [b], Hossam Ghoneim [c], Amr Abul-Fotouh [b], Gamal Esmat [b]

[a] Department of Pathology, Faculty of Medicine, Cairo University, Cairo, Egypt
[b] Department of Endemic Medicine and Hepatology, Faculty of Medicine, Cairo University, Cairo, Egypt
[c] Department of Tropical Medicine and Hepatology, Faculty of Medicine, Beni-Sueif University, Beni Sueif, Egypt

ARTICLE INFO

Article history:
Received 29 January 2014
Accepted 23 June 2015

Keywords:
HCV
Genotype 4
ALT
AST

ABSTRACT

Background and study aims: Worldwide, Egypt has a high prevalence of adult hepatitis C virus (HCV) infection. Serum alanine aminotransferase (ALT) activity is most commonly measured to assess hepatic disease. The revision of the definition of the normal limits for the ALT level is advisable. The aim of this work was to compare the histopathological changes in the liver tissue biopsies of HCV-infected patients, clinically presenting with ALT levels below normal, based on the conventional, previously used upper limit of normal (ULN) of ALT (40 U/L for men and 30 U/L for women) with the proposed new ULN (30 U/L for men, and 19 U/L for women).

Patients and methods: This is a retrospective cross-sectional study. A total of 668 cases of chronic hepatitis C genotype 4 were included. Patients were classified according to grades of histological activity and fibrosis stages (by the Metavir scoring system). They were also classified into normal and high groups according to the old and new cutoffs of both aspartate transaminase (AST) and ALT levels.

Results: The results of our study showed that the serum AST level in our study showed a better correlation with the histopathological changes in liver biopsy rather than ALT, especially when using the old cutoff of the ULN for AST. The serum ALT level in our study (both the old and the new cutoffs) did not show a significant correlation with the histopathological status in the liver biopsies of our patients.

Conclusion: This study concluded that the old cutoff of the ULN AST is a better predictor of fibrosis.

Introduction

Hepatitis C virus (HCV) infection is a major global public health problem [1]. Worldwide, Egypt has a high prevalence of HCV infection, averaging 15–25% in rural communities, mainly genotype 4 [2].

In patients with chronic hepatitis, liver biopsy is useful in determining the nature and extent of hepatic injury. The degree of inflammation, the type of inflammatory cells, the demonstration of intrahepatic viral antigens and their localisation, and the distribution of fibrosis can provide information relevant to the natural history of disease, diagnosis, prognosis, relative urgency of therapy, and response to treatment [3,4].

Serum alanine aminotransferase (ALT) activity is most commonly measured to assess the severity of hepatic disease. However, approximately 30% of patients with chronic HCV infection show persistently normal alanine aminotransferase (PNALT) levels, and these patients were historically excluded from treatment [5].

In patients with chronic HCV infection, revision of the definition of normal limits for the ALT level is advisable as the current standards for "normal" ALT level are defined using populations with subclinical liver disease, thus failing to identify many patients with hepatic injury. The new definitions of normal range for ALT are more accurate and sensitive in diagnosing early liver injury, thus minimising health-related morbidity. The new upper limit of normal (ULN) for ALT (30 U/L for men and 19 U/L for women) is substantially lower than the levels that laboratories currently consider to be the upper range of normal (40 U/L for men and 30 U/L for women) [5,6].

The aim of this work was to compare the histopathological changes in the liver tissue biopsies of HCV-infected patients, presenting clinically with ALT levels below normal, based on the conventional, previously used ULN of ALT (40 U/L for men and 30 U/L for women) with the proposed, new ULN (30 U/L for men and 19 U/L for women).

* Corresponding author.
E-mail address: ma_mohey@yahoo.com (M.A. Mohey).

http://dx.doi.org/10.1016/j.ajg.2015.06.004
1687-1979/

Patients and methods

This is a retrospective cross-sectional study. The data of patients with chronic HCV infection were collected from the archives of two centres, namely the pathology department at the Kasr el Aini Hospital, Cairo University, and the Fatemic Cairo hospital, which is one of the viral hepatitis treatment centres affiliated to the National Committee for Control of Viral Hepatitis, Ministry of Health. After selection of cases according to our inclusion criteria, 668 patients were included. The approval of the Cairo University review board was obtained.

The patients included in the study were of either sex, aged from 18 to 70 years, positive for HCV antibodies genotype 4, and positive for HCV RNA by qualitative polymerase chain reaction (PCR). Serum levels of Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were determined by using Dimension analyser (Dade Behring, USA).

All patients signed the consent forms demonstrating the possible risk factors of the percutaneous liver biopsy procedure. Biopsies <1 cm in length and those with less than six portal tracts were also excluded. Ultrasound-guided percutaneous liver biopsies were obtained using a Medax (Poggio Rusco, Italy) 16 GX 200-mm single-step biopsy needle. The percutaneous liver biopsies were fixed in 10% neutral formalin, processed, then embedded in paraffin, and sliced into 5-μm-thick sections. The histological sections were stained with haematoxylin and eosin, and Masson's trichrome stains. The liver sections were evaluated by a single pathologist who was blinded to the patients' clinical and laboratory data. The degree of inflammatory reaction and the stage of fibrosis were evaluated according to the Metavir scoring system [7].

Statistical methods

Patients were classified according to grades of histological activity and fibrosis stages (by the Metavir scoring system). They were also classified into normal and high groups according to the old and new cutoffs of both aspartate transaminase (AST) and ALT. Spearman correlation was used to correlate fibrosis stages with other laboratory results and with enzyme levels (normal and high) according to the old and proposed new cutoffs, respectively.

Results

As for the sex of our patients, 82% were males (548 patients), whereas 18% were females (120 patients). The mean age of the patients was 40 years (±9.86). The age of male patients was 39.81 years (±9.68), ranging from 18 to 60 years, whereas the age of female patients was 43.28 years (±10.25), ranging from 20 to 59 years. All of the patients included in our study were infected with genotype 4 HCV. The mean body mass index of the patients was 28.1 (±4.24), ranging from 18 to 25. Fig. 1 shows the inflammatory activity and fibrosis stage in the liver biopsies. There is a statistically significant correlation between activity and fibrosis in the liver biopsies of the studied patients ($P < 0.01$, Spearman correlation coefficient = 0.72) (Fig. 2).

Table 1 shows that there is a statistically significant correlation between activity grades and AST levels according to both the old conventional and proposed new cutoffs ($P < 0.05$, Spearman correlation coefficient = 0.23 and 0.10, respectively). Table 2 shows that there is a statistically significant correlation between fibrosis stage and AST levels according to both the old conventional and proposed new cutoffs ($P < 0.05$, Spearman correlation coefficient = 0.24 and 0.13, respectively).

Discussion

In this study, inflammatory activity seemed to increase concomitantly with fibrosis with no gender difference. This is in keeping with the findings of Lu et al. (2003) and Kleiner (2005) [8,13]. However, these results are in discordance with those of El Hawary et al. (2007) and Poynard et al. (2001), who concluded that there was little or no correlation between the severity of the necro-inflammatory activity and the degree of fibrosis [14,15].

About 35% of the HCV-infected patients studied have advanced fibrosis and about 6% have cirrhosis. El Hawary et al. (2007) found that 25% of their cases had advanced fibrosis, and three out of 43 cases (about 7%) had cirrhosis [14]. Holemberg et al. found that 38% of their patients had advanced fibrosis [16]. In another study conducted in 150 patients, 97% were genotype 4. Gabr and Alghadir found that 60% of their patients had advanced fibrosis and 20% had liver cirrhosis [17].

The results concluded that both inflammatory activity and fibrosis stage did not differ significantly between the two groups, with respect to the proposed, new and conventional, old cutoffs. In this study, the AST enzyme proved to be a surrogate marker of fibrosis. In concordance with our results, Al Ashgar et al. (2009) demonstrated that a lower AST level reflects less severe histological parameters [17]. Furthermore, Assy and Minuk (2000) found that serum AST values emerged as the most important predictive variable of histological inflammatory activity and fibrosis. The investigators found that serum ALT values did not correlate with histological activity, but they did correlate weakly with the extent

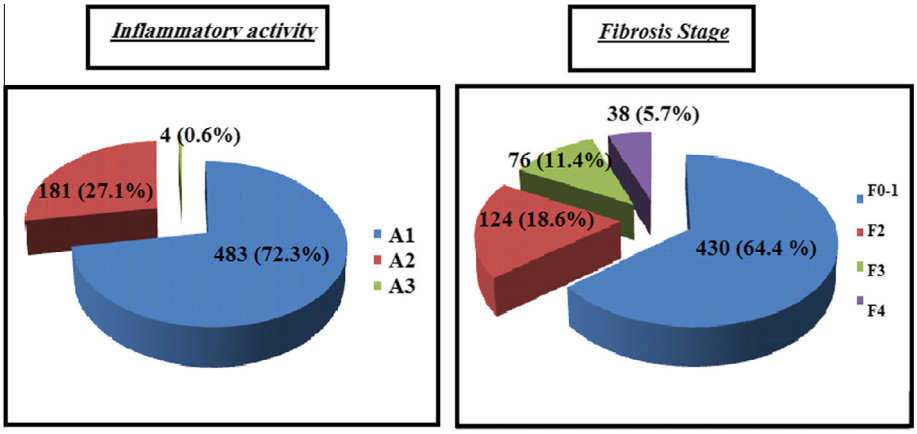

Fig. 1. Inflammatory activity and fibrosis stage in liver biopsies.

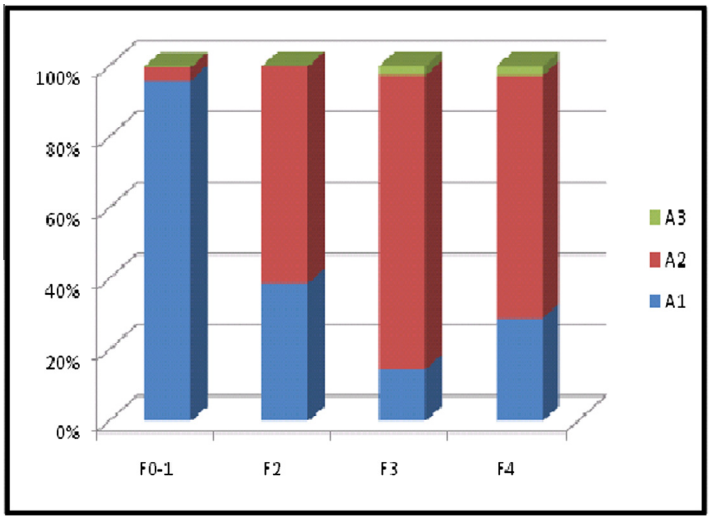

Fig. 2. Correlation between activity and fibrosis in liver biopsies.

Table 1
AST and ALT levels in relation to activity.

		A1	A2	A3	Total	Spearman correlation coeff.	*P*-value
AST (Old cutoff)[a]	Normal	234 (48.4%)	43 (23.7%)	0 (0%)	277 (41.2%)	0.23	<0.01*
	High	249 (51.6%)	138 (76.24%)	4 (100%)	391 (58.8%)		
AST (New cutoff)[b]	Normal	83 (17%)	17 (9.4%)	0 (0%)	100 (14.9%)	0.10	0.04*
	High	400 (83%)	164 (90.6%)	4 (100%)	568 (85.1%		
ALT (Old cutoff)[a]	Normal	157 (32.1%)	41 (22.9%)	1 (25%)	199 (29.6%)	0.09	0.08**
	High	326 (67.9%)	140 (77.1%)	3 (75%)	469 (70.4%)		
ALT (New cutoff)[b]	Normal	71 (14.6%)	16 (8.8%)	0 (0%)	87 (13.1%)	0.08	0.12**
	High	412 (85.4%)	165 (91.2%)	4 (100%)	581 (86.9%)		

[a] 40 U/L for men and 30 U/L for women [5,6].
[b] 30 U/L for men and 19 U/L for women.
* Significant.
** Nonsignificant.

Table 2
AST and ALT levels in relation to fibrosis.

		F0–1	F2	F3	F4	Total	Spearman correlation coeff.	*P*-value
AST (Old cutoff)[a]	Normal	214 (49.9%)	37 (29.8%)	17 (22.4%)	8 (21.1%)	276 (41.4%)	0.24	<0.01*
	High	216 (50.1%)	87 (70.2%)	59 (77.6%)	30 (78.9%)	392 (58.6%)		
AST (New cutoff)[b]	Normal	79 (18.4%)	10 (8.1%)	5 (6.6%)	4 (10.6%)	98 (14.7%)	0.13	0.01*
	High	351 (81.5%)	114 (92%)	71 (93.4%)	34 (89.4%)	570 (85.3%)		
ALT (Old cutoff)[a]	Normal	144 (33%)	32 (25.9%)	17 (23.7%)	7 (18.4%)	200 (29.9%)	0.11	0.06**
	High	286 (67%)	92 (74.1%)	59 (76.3%)	31 (81.6%)	468 (70.1%)		
ALT (New cutoff)[b]	Normal	63 (14.6%)	14 (11%)	7 (9.2%)	3 (7.9%)	87 (13%)	0.37	0.07**
	High	367 (85.4%)	110 (89%)	69 (90.8%)	35 (92.1%)	581 (87%)		

[a] 40 U/L for men and 30 U/L for women.
[b] 30 U/L for men and 19 U/L for women.
* Significant.
** Nonsignificant.

of hepatic fibrosis [18]. In a study of predominantly genotype 4 patients, Hasan et al. (2002) found that the mean inflammatory and fibrosis scores were similar in patients with normal and elevated ALT levels [19]. In a cross-sectional study, Marcellin et al. (2002) claimed that the serum ALT levels correlated weakly with disease activity and minimally or not at all with hepatic fibrosis [3].

Finally, we conclude that the serum AST level showed a better correlation with the histopathological changes in liver biopsy rather than ALT, especially when using the old cutoff of the ULN for AST. The serum ALT level in our study (both the old and the new cutoffs) did not show a significant correlation with the histopathological status in the liver biopsies of our patients.

Conflicts of interest

The authors declared that there was no conflict of interest.

References

[1] Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus in the United States. N Engl J Med 1999;341:556–62.

[2] El-Raziky MS, El-Hawary M, Esmat G, et al. Prevalence and risk factors of asymptomatic hepatitis C virus infection in Egyptian children. World J Gastroenterol 2007;13(12):1828–32.
[3] Marcellin P, Asselah T, Boyer N. Fibrosis and disease progression in hepatitis C. Hepatology 2002;36:S47–56.
[4] Friedman L. Controversies in liver biopsy. Liver diseases in the 21st century: clinicopathological correlates. American association for the study of liver disease. Postgraduate course 2003; 233:238.
[5] Prati D, Taioli E, Zanella A, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med 2002;137(1):1–10.
[6] Van der Poorten D, Kenny DT, Butler T, George J. Liver disease in adolescents: a cohort study of high-risk individuals. Hepatology 2007;46:1750–8.
[7] Bedossa P, Poynard T. The METAVIR cooperative study group. An algorithm for the grading of activity in chronic hepatitis. Hepatology 1996;24:289–93.
[8] Lu LG, Zeng MD, Wan MB, et al. Grading and tagging of hepatic fibrosis, and its relationship with non-invasive diagnostic parameters. World J Gastroenterol 2003;9:5574–8.
[13] Kleiner DE. The liver biopsy in chronic hepatitis C: a view from the other side of the microscope. Semin Liver Dis 2005;25:52–64.
[14] El-Hawary MA, El-Raziky MS, Esmat G, et al. Assessment of hepatic fibrosis in pediatric cases with hepatitis C virus in Egypt. World J Gastroenterol 2007;13(20):2846–51.
[15] Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis c. J Hepatol 2001;34:730–9.
[16] Holmberg SD, Lu M, Rupp LB, et al. Non invasive serum fibrosis markers for screening and staging chronic hepatitis C virus patients in a large US cohort. Clin Infect Dis 2013;57(2):240–6.
[17] Gabr SA, Alghadir AH. Prediction of fibrosis in hepatitis C patients: assessment using hydroxyproline and oxidative stress biomarkers. Virusdisease 2014;25(1):91–100.
[18] Al Ashgar H, Helmy A, Khan MQ, et al. Predictors of sustained virological response to 48-week course of pegylated interferon alfa-2a and Ribavirin in patients infected with hepatitis C genotype 4. Ann Saudi Med 2009;29(1):4–14.
[19] Assy N, Minuk GY. Serum aspartate but not alanine aminotransferase levels help to predict the histological features of chronic hepatitis C viral infections in adults. Am J Gastroenterol 2000;95(6):1545–50.