The Severity of the Clinical Expression of Lysosomal Acid Lipase in Patients with Cryptogenic Cirrhosis

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Abstract: Lysosomal acid lipase is an enzyme that intervenes in the last steps of lipid metabolism to hydrolyze cholesteryl esters. Patients with cryptogenic cirrhosis present a clear deficiency of lysosomal acid lipase with an unknown mechanism. Design: The present study has an analytical and retrospective design, of a sample of 55 patients with cryptogenic cirrhosis. The degree of association of lysosomal acid lipase was determined with the results of the enzymes alanine aminotransferase and alkaline phosphatase, as well as with the clinical manifestations of portal hypertension and splenic volume. The sensitivity and specificity of the test were determined for the diagnosis of the manifestations of portal hypertension. Results: The most frequent complication of portal hypertension was variceal hemorrhage with 40%, followed by ascites with 32.7%, and last, by hepatic encephalopathy, with 18.2%. Association by the x² test was without statistical significance with values of 0.177, 0.299, and 0.184 for encephalopathy, variceal hemorrhage, and ascites, respectively. The association of lysosomal acid lipase and splenic volume utilizing the Student t-test had a low degree of association and p >0.05. Through ROC curves, we obtained AUROC results close to 0.5. Conclusion: It is established that there is no correlation of the levels of activity of lysosomal acid lipase with the values of alanine aminotransferase and alkaline phosphatase, as well as with the presence or absence of clinical manifestations and by ultrasound of portal hypertension. Lysosomal acid lipase is not a good test for the diagnosis of the clinical manifestations of portal hypertension.

Keywords: Lysosomal Acid Lipase, Cryptogenic Cirrhosis, Portal Hypertension, Liver Cirrhosis, Liver Cirrhosis

1. Introduction

Liver cirrhosis is considered a global public health problem with an increasing prevalence at a worldwide level, due to greater recognition of the diagnosis and the associated risk factors. Liver cirrhosis has an estimated prevalence in the North-American population of 0.27% [1] and a prevalence in the Latin population of chronic liver disease (CLD) of 61.1% [2]. CLD-associated mortality increased by 46% at the global level during the period comprising 1980-2010 and it is between the first 11 causes of death in
The prevalence of PH in patients with CLD and LALD has not been established by means of imaging studies [20]. LALD is being frequently documented in NAFLD, NASH, hepatic patients with cholesteryl ester storage disease (CESD) are most frequently defined extra-hepatic manifestations are hepatomegaly (99.3%) and splenomegaly (74%) [18], and the complications of portal hypertension (PH), and among these, aminotransferase (ALT) and alkaline phosphatase (ALP) esophageal varices [18-19]. Also, the increase in alanine have been associated with CESD [18]. The greater hypercholesterolemia phenotype similar to type IIa or type-IIa hypercholesterolemia-associated hepatopathies makes difficult its clinical study, particularly in those patients who were discarded were those with comorbidities or complications (cardiac failure, hematological cancer, etc.) that were susceptible to modify the results of the variables and increase the biases, and those who had died during hospitalization due to other causes rather than PH findings.

2.1. Primary and Secondary Endpoint

The correlation was carried out of the activity levels of LAL with ALT and ALP. Similarly, the degrees were established of LAL with PH, such as ascites, variceal bleeding, and hepatic encephalopathy, in addition to the correlation between LAL levels and the splenic ultrasound findings. Later, we estimated the sensitivity and specificity of the LAL test as the diagnostic value in the manifestations of PH with ROC curves.

2.2. Statistical Analysis

The results are represented as mean and the categorical variables, with an “n” (%). We determined the normality of the variable by means of the Kolmogorov-Smirnov test for LAL (t=0.145; p >0.05), ALT (t=0.354; p >0.05), ALP (t=0.173; p >0.05), and splenic volume (t=0.147; p >0.05).

The independent association was effected of the variables ALT, ALP, and splenic volume with LAL using the Pearson correlation and afterward by linear multiple regression analysis. To prove whether there was an association between the categorical variables of portal hypertension and the categorized LAL variable-under-study, we utilized the Fisher exact test. For the analytical correlation model between LAL and the clinical manifestations of PH, we conducted binary logistic regression analysis. Later, we developed ROC curves for the test of LAL with the complications of PH.

3. Results

Table 1 presents the demographic and biochemical characteristics of the study’s entry population, in which it is observed that 55 patients, as well as the main results of the correlations (women n=48, and men n=7), were distributed by sex and age with the following results (male: female ratio 1:7, and mean age 58.93±12.56 years). We conducted the t-test of the mean of our variables of one sample with the mean of Vespasiani-Gentilucci, et al. [12], obtaining for LAL a t=-10.088; p=0.005. With this, it is established that the mean of LAL activity is significantly less. In the same manner, we performed the same analysis with splenic volume,
obtaining a $t=-6.300$; $p=0.005$, which corresponds to that a splenic volume of the population of our work is significantly less than in the enzyme ALT, in which a $t=2.113$; $p=0.02$ was obtained, with which it is concluded that the mean of ALT is significantly greater than in our sample.

### Table 1. Main characteristics of the study population and correlations.

| Variable               | N=55 | Mean          | Correlation | p     |
|------------------------|------|---------------|-------------|-------|
| LAL* (nmol/spot/h)     | 350.03±203.80 |               |             |       |
| Age (years)            | 58.93±12.56   | 0.234         | <0.05       |       |
| ALTβ (IU/L)            | 90.07±168.32  | 0.079         | 0.282       |       |
| ALP¶ (UI/L)            | 176.78±95.27  | -0.139        | 0.394       |       |
| Splenic volume (mm)    | 505.33±212.51 | -1.42         | 0.738       |       |
| Collateral circulation | 23 (39.65%)    |               |             |       |
| INR†                   | 1.26±0.21     |               |             |       |
| BMI‡                   | 28.9±4.15     |               |             |       |
| Hepatic encephalopathy |       | $X^2=474$     | 0.093       |       |
| Ascites                |       | $X^2=2.018$   | 0.365       |       |
| Variceal bleeding      |       | $X^2=0.925$   | 0.63        |       |

*LAL; Lysosomal Acid Lipase, βALT; Alanine aminotransferase, ¶ALP; Alkaline phosphatase, †INR; International Normalized Ratio, ‡BMI; Body Mass Index.

The enzyme ALT does not present a clinically significant correlation with the variability of LAL (95% CI $r=0.234$; $p<0.05$) and, for its part, ALP does not present a clinical correlation nor statistical significance (95% CI $r=0.079$; $p=0.282$). The correlation of splenic volume with LAL resulted without statistical significance and with a low degree of correlation ($r=-0.139$; $p=0.394$).

The proportion of complications associated with PH in the first place was variceal hemorrhage with 40%, followed by ascites with 32.7%, and last, hepatic encephalopathy with 18.2%. A total of 65.5% of patients with esophageal varices were classified with enlarged varices of the Baveno classification. The linear multiple regression analysis of an $r=0.395$, with an adjusted R of 0.31 (31%), explains 31% of the variation of the manifestations of portal hypertension in turn explained by LAL variability.

The LAL variable was categorized with a cut-off point of $>500$ and of $<500$ nmol/spot/h, obtaining one for hepatic encephalopathy of 100% and a specificity of 17.8%, for variceal bleeding a sensitivity of 90.9%, and a specificity of 18.2% and, last, a sensitivity of 94.4%, and a specificity of 18.9%. Patients with CC did not have a greater frequency of hepatic encephalopathy as the values diminished of LAL, the study LAL (81.81% vs. 18.18%; $p=0.177$), similarly in patients with ascites (67.3% vs. 32.7%; $p=0.184$) and with variceal hemorrhage (59.99% vs. 39.99%, $p=0.299$).

The binary logistic model was not statistically significant with a $X^2=4.74$; $p=0.093$ for hepatic encephalopathy, $X^2=2.018$; $p=0.365$ for ascites, and $X^2=0.925$; $p=0.63$ for variceal bleeding. Afterward, employing ROC curves, we obtained the following results: for variceal hemorrhage, 0.517, hepatic encephalopathy, 0.333, and for ascites, 0.429, concluding that this is not a good diagnostic test for the clinical manifestations of portal hypertension (Figures 2-4).
4. Discussion

Liver cirrhosis is a public health problem at the worldwide level due to its high economic costs in diverse sectors, mainly in the health and labor sector [4, 7, 27]. In 2004, it was found to be the third cause of cirrhosis in Mexico and, as in the rest of the studies, women were those majorly affected [4, 11]. In our study, the proportions of affection by gender in patients with CC were maintained, because women constituted 87.3% (n=48) of our total sample. In the study by Rinaldi, et al., the most frequent complications of PH in patients with CC were ascites with 54.9%, followed by hepatic encephalopathy with 25.5%, and last, variceal bleeding with 6.9% [28], in contrast with our population, in which variceal hemorrhage was the most frequent complication with 40%, followed by ascites with 32.7% and hepatic encephalopathy with 18.2%. The importance of the latter lies in that variceal hemorrhage is the complication associated with greater mortality; our patients have been documented with esophageal varices, classifying enlarged varices according to the classification of Baveno. The lipid-limiting enzyme LAL is found diminished in multiple chronic hepatic disorders [11], and CC is the hepatic affectation with the greatest diminution of LAL compared with other etiologies [11, 12]. Although the results of Vespasiani-Gentilucci, et al. describe that, according to the diminution of the enzyme LAL, patients present data of lesser severity. Nonetheless, the state of severity is not well-defined through the severity scale [12]. Mean LAL in patients with NAFLD was 530 nmol/spot/h [19], and mean LAL in CC according to our results was 350.03 nmol/spot/h. Similarly, in the statistical analysis, the mean LAL in our population is significantly less in comparison with the mean of the sample of Vespasiani-Gentilucci, et al [12]. On the other hand, the enzyme ALT is significantly greater than the mean of those same authors, and the splenic volume of our population is lower; therefore, these changes could be the cause of obtaining different results and probably due to that, in Mexico, there is a greater number of patients with obesity, metabolic syndrome, and diabetes than in the population of Italian origin [12]. Patients with CC are frequently diagnosed at earlier disease stages than those with CH due to other etiologies [28], this is congruent with our results because our team demonstrated that 46 subjects in the sample were found in Child-Pugh class A-B. According to the study published by Bernstein, et al. patients with LALD are associated with a rise in ALT and AST [18], while in our results, mean ALT and ALP were found increased: the diminution of the LAL enzyme in patients with CC had no correlation with the increase of ALT and ALP, concluding that the diminution of LAL does not entail the measurement of hepatic enzymes. With the latter, the result was not able to be validated as compared with that of Bernstein, et al CC is a diagnosis of exclusion that, in a not-at-all negligible percentage, is due to NAFLD [18]; likewise, the enzyme LAL, while very much below the mean of other works on Mexican population, appears to have no relation with the variability of the hepatic profile, manifestations of portal hypertension, and splenic volume.
patients with reduced LAL activity levels due to an increase in the principal cause of PH is cirrhosis, patients with NAFLD initiate between the correlation of LAL and the enzymes alanine aminotransferase and the alkaline phosphatase, as well as the complications of PH. The enzyme LAL is not a good test for the diagnosis of the clinical manifestations of PH.

In our population, the most frequent complication of portal hypertension was variceal bleeding, in contrast with other works in patients with cryptogenic cirrhosis. Therefore, it would be important to recognize which are the risk factors that increase the rate of variceal hemorrhage in our population, because this complication is considered as that of greatest mortality in patients with liver cirrhosis. Scarcie investigation in patients with cryptogenic cirrhosis, since it is a diagnosis of exclusion and given that it could easily be a manifestation of another pathology without being able to arrive at the etiological diagnosis, makes the studies entertain broad variability in their results; thus, it would be difficult to validate the publication.

5. Conclusions

It is established that there was no statistical significance between the correlation of LAL and the enzymes alanine aminotransferase and the alkaline phosphatase, as well as the complications of PH. The enzyme LAL is not a good test for the diagnosis of the clinical manifestations of PH.

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Conflicts of Interest

There are no conflicts of interest.

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