Correlations between the value of serum cholinesterase and Child-Pugh and Meld-Na scores in cirrhotic patients

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ABSTRACT

Many laboratory tests are utilised in the evaluation of the hepatic functions. Serum cholinesterase has a low serum value in liver dysfunction in contrast with other enzymes. The aim of the study was to assess the value of serum cholinesterase in evaluation of the liver reserve function in cirrhotic patients. A total of 70 patients were divided into 3 groups according to the Child-Pugh Score. Using correlation analysis, the correlation between serum cholinesterase and albumin and International Normalized Ratio time was analysed. Cirrhotic patients were divided into A, B and C grades as per Child-Pugh score. The results showed that cholinesterase levels tend to decrease according to the Child-Pugh score, highest in the A group and lowest in the C group. The cholinesterase correlated with the albumin serum levels, value of Child-Pugh score and MELD-Na score and did not correlate to INR. In conclusion, correlated with the damage severity of the liver cells cholinesterase may respond to liver reserve function.

Keywords: serum cholinesterase, liver cirrhosis, Child-Pugh Score, albumin, MELD-Na score

INTRODUCTION

Laboratory tests, often known as liver function tests (LFTs), are used in the evaluation and treatment of patients with liver disease, comprising serum aspartate and alanine transaminases, alkaline phosphatase, bilirubin and albumin [1]. These tests often reveal abnormal results in patients with clinical problems other than liver dysfunction [2]. Tests of biosynthetic capacity of the liver include serum albumin, ceruloplasmin, ferritin, alfa1-antitrypsin, lipoproteins and blood clotting factors. These substances are synthesised in the liver and transported into the circulation. Cholinesterase is synthetised almost all in the hepatocytes and it is released into the bloodstream [5]. Serum cholinesterase activity is lower in liver dysfunction due to reduced synthesis. This contrasts with other serum enzymes used in the clinical assessment of liver function whose activities increase because of enhanced release from their cellular sources following cell membrane damage [3] or secondary to treatment. In gastroenterology, the Child-Pugh score (also known as the Child-Turcotte-Pugh score) is used to assess the prognosis of chronic liver disease, mainly cirrhosis. Originally
was used to predict surgery related mortality, the Child Pugh score is now used to predict prognosis as well as the required intensity of treatment, and the necessity for liver transplantation. Two main clinical measures in Child-Pugh score, serum protein and blood-clotting factors are essential in evaluating the liver reserve function of cirrhotic patients [4]. However, the cirrhotic patients, particularly those with advanced liver disease, Child grades B and C with ascites or haemorrhagic tendency, are usually treated with albumin or blood transfusions, which may affect the real numeric value for calculating the Child-Pugh Score [5]. Additionally, serum cholinesterase is not affected by this treatment. We compared serum cholinesterase with the Child-Pugh score and MELD-NA score to evaluate the liver reserve function of cirrhotic patients. Since serum cholinesterase, albumin and blood-clotting factors are synthesized by the liver with different half-life [6], we also monitored the correlation between cholinesterase, albumin and INR.

PATIENTS AND METHODS

Patients

A total of 70 patients presenting to the Fundeni Clinical Institute (Bucharest, Romania), 28 male medium age and 42 females between 2017 and 2018 were included in the present study. Inclusion criteria for the study were: a diagnosis of liver cirrhosis based on histology, clinical or ultrasonographic signs or on transient elastography (FibroScan, EchoSens, Paris, France). Exclusion criteria were history of albumin or blood transfusion in the last 4 weeks prior to enrolment, clinical evidence of variceal bleeding at enrolment, history or clinical evidence of hepatocellular carcinoma and history of liver transplantation. Informed consent was obtained from patients included in the study.

Measurement of biochemical serum markers

Blood samples were collected with minimal venostasis. Serum was obtained from clotted blood by centrifugation within 1 h from sampling. LFTs comprising serum albumin and INR were carried out. Serum cholinesterase activity was determined using a chemiluminescent method using a Cobas e601 Roche automatic analyser in 2 hours of sample separation.

Statistical analysis

Database management and statistical analysis were performed using JASP 0.16.3 Software for Windows. Descriptive results were expressed as the mean ± standard deviation (SD) or number (percentage) of patients with a condition. Multiple comparisons for the ANOVA test were used to compare the mean data. The Pearson correction test was applied for comparison of cholinesterase, albumin and serum prothrombin times (INR). The tests were two-tailed and P<0.05 was considered to indicate a statistically significant difference.

RESULTS

Patient characteristics

A total of 70 patients mean age 66.47±10.41 years were included. 28 patients were male with a mean age of 63.64±12.74 Years and 42 females with a mean age of 68.35±8.15 years. The main demographic data of the patients are summarized in Table 1 and the clinical and laboratory data in Table 2.

Child-Pugh class A group was present in 43 patients (61.42%), class B in 13 patients (18.57%) and class C in 14 patients (20%) (Table 3).

Serum cholinesterase in various Child-Pugh score groups

The cirrhotic patients were strictly grouped into A, B and C groups, based on their Child-Pugh score. The results showed that serum cholinesterase tended to decrease significantly in the three grades: Child A (8055.46±1709.09 U/l), Child B (5415.76±1109.27 U/l) and Child C (2543.64±838.51 U/l) (Table 4). Difference between the mean serum cholinesterase activity in the Child A, B and C groups was statistically significant, as was the difference between the mean values for the Child B and C groups (Table 3, Figure 1, Figure 2).

Correlation between the serum cholinesterase, albumin and INR

Cholinesterase was positively correlated with albumin (r=0.633, P<0.001) and negatively correlated with INR (r=-0.404, P<0.001) in the cirrhotic patients, confirming that those substances were synthesized in the liver and reduced in the liver dysfunction due to reduced synthesis. Cholinesterase and INR (r=-0.404, p=0.001) have a negative strong correlation. Albumin and INR (r=0.782, p=0.001) have a strong positive correlation (Table 4, Table 5, Table 6).

TABLE 1. Demographic characteristics of the study population

|                | Valid | Missing | Mean   | Std. Deviation | Minimum | Maximum |
|----------------|-------|---------|--------|----------------|---------|---------|
| Age female     | 42    | 0       | 68.357 | 8.150          | 46.000  | 84.000  |
| Age male       | 28    | 0       | 63.643 | 12.749         | 33.000  | 82.000  |
TABLE 2. Clinical and laboratory characteristics of the study population

| Descriptive Statistics | Valid | Missing | Mean | Std. Deviation | Minimum | Maximum |
|------------------------|-------|---------|------|----------------|---------|---------|
| Age                    | 70    | 0       | 66.471 | 10.416         | 33.000  | 84.000  |
| Sex                    | 70    | 0       | 3.471  | 1.046          | 1.800   | 5.200   |
| Albumin                | 70    | 0       | 6462.871 | 2651.086     | 1131.000 | 11982.000 |
| Child Pugh Score       | 70    | 0       | 7.157  | 7.089          | 6.000   | 32.000  |
| MELD-Na Score          | 70    | 0       | 2.572  | 5.592          | 0.270   | 30.900  |
| Total Bilirubin        | 70    | 0       | 0.371  | 0.705          | 0.000   | 2.000   |
| Encephalopathy grade   | 70    | 0       | 0.300  | 0.667          | 0.000   | 2.000   |
| Ascites grade          | 70    | 0       | 0.950  | 0.402          | 0.400   | 3.300   |
| Creatinine             | 70    | 0       | 63.029 | 38.464         | 11.000  | 190.000 |
| ALAT                   | 70    | 0       | 1.243  | 0.434          | 0.890   | 3.010   |
| Na                     | 70    | 0       | 137.971| 5.217          | 122.000 | 147.000 |
| Hb                     | 70    | 0       | 13.523 | 6.261          | 12.000  | 22.000  |
| PLT                    | 70    | 0       | 176.443| 75.188         | 31.000  | 348.000 |
| Leu                    | 70    | 0       | 6.599  | 2.473          | 3.100   | 18.000  |

Note. Not all values are available for Nominal Text variables

TABLE 3. Cholinesterase activity in the Child-Pugh groups of cirrhotic patients

| Descriptive Statistics | Cholinesterase activity |
|------------------------|-------------------------|
|                        | A  | B  | C  |
| Valid                  | 43 | 13 | 14 |
| Missing                | 0  | 0  | 0  |
| Mean                   | 8055.465 | 5415.769 | 2543.643 |
| Std. Deviation         | 1709.092 | 1109.270 | 838.512 |
| Range                  | 6719.000 | 2950.000 | 2820.000 |
| Minimum                | 5263.000 | 4342.000 | 1131.000 |
| Maximum                | 11982.000 | 7292.000 | 3951.000 |

Correlation between the serum cholinesterase, Child-Pugh Score and MELD-Na

Cholinesterase and Child-Pugh Score have a negative, strong correlation (r=-0.696, p=0.001). Cholinesterase and MELD-Na score (r=-0.548, p=0.001) have the same negative strong correlation. Between the Child-Pugh score and MELD-Na score (r=-0.783, p=0.001) we have a strong significative correlation that validates the data (Table 4, Table 5, Table 6, Table 7).
**Table 7.** Correlations between cholinesterase, albumin and INR in all patients

| Related pairs       | Correlation index | P-value |
|---------------------|-------------------|---------|
| BCHE: Alb           | r=0.663           | 0.001   |
| BCHE: INR           | r=-0.404          | 0.001   |
| Alb: INR            | r=0.782           | 0.001   |
| BCHE: Child-Pugh Score | r=-0.696       | 0.001   |
| BCHE: Meld NA       | r=-0.584          | 0.001   |
| Child-Pugh Score: Meld-Na score | r=0.783 | 0.001   |

**Discussion**

In biochemistry, cholinesterase is part of a family of enzymes that process the neurotransmitter acetylcholine into choline and acetic acid, a reaction necessary to allow a cholinergic neuron to return to its resting state after activation [7]. There are two types of cholinesterases: acetylcholinesterase (AChE), also known as RBC and erythrocyte cholinesterases or acethylene acetylhydrolase, found primarily in the blood and neural synapses. AChE exists in various molecular forms. Pseudocheolinesterase, also termed as plasma cholinesterase (BCHE), butyrylcholinesterase or acylcholine acylhydrolase, is found primarily in the liver [8,9].

Estimation of the level of activity of the cholinesterase found in serum was first suggested by McArindle in 1940 [10], as a useful means for differentiating hepatic from post hepatic jaundice. The evidence which has accumulated suggests that cholinesterase activity is an assessment indicator for liver function in patients with liver disease. In China, cholinesterase has been included in scores to distinguish hepatitis severity by society of liver disease [11]. However, few studies are available regarding the value of cholinesterase in evaluating liver reserve function in cirrhotic patients. The Child-Turcotte-Pugh scoring system is the first of its kind in stratifying seriousness of end-stage liver disease, mainly cirrhosis [12]. In our study 70 patients were grouped into A, B and C grades, as per Child-Pugh score. The results show that cholinesterase tended to significantly decrease in the three grades. In the Child A group, the value of serum cholinesterase was 8055.46U/l with a SD of 1709.09U/l, in the Child B group the mean value of serum cholinesterase was 5415.76U/l with SD of 1109.27 and in the Child C the mean value of serum cholinesterase was 2543.64U/l with a SD of 838.51U/l. The result agrees with the findings of Gu and Zhong [13]. Their data demonstrated that the levels of cholinesterase in the three grades were: Child A (5978±535U/l), Child B (3957±454U/l) and Child C (2267±332U/l). The Child-Pugh score is calculated from the values of five clinical measures of liver disease, among which ascites and encephalopathy are subjective measures [14]. Liver cirrhosis is classified into Child-Pugh class A-C, employing the added score from above. Compared with the Child-Pugh score, cholinesterase has the advantage that it is easier and more objective in evaluating the liver reserve of cirrhotic patients.

The liver performs an important role in protein biosynthesis. Cholinesterase, albumin and blood-clotting factors are synthesized in the liver than transported into the circulation. Thus, LFT’s include cholinesterase, albumin and prothrombin time (INR) and may provide useful information concerning the state of a cirrhotic patient’s liver. In our study, in cirrhotic patients, cholinesterase was positively correlated with albumin and negatively correlated with INR, confirming that those substances were synthesized by the liver and reduced in liver dysfunction due to reduced synthesis.
sated cirrhotic patients, albumin and blood transu-

sions are usually used, which may affect the real

numerical value to calculate the Child-Pugh score [15]. If surgery is needed as a treatment the risk cal-

culated on the Child-Pugh score may be inaccurate if the patient received treatment [16]. In their study,

Gu and Zhong [13] demonstrated that three cirrhot-

ic patients (two Child B and one Child A score pa-

tient) suffered hepatic encephalopathy following

portal azygos disconective operation, with cho-

linesterase levels of under 2000U/l. Thus, those au-

thors suggested that cirrhotic patients with cho-

linesterase <2000U/l may have higher risk for liver

failure, if undergoing abdominal surgery. Thus, the

combination of Child-Pugh score may be more sub-

jective and accurate in evaluating the liver reserve

function of cirrhotic patients.

CONCLUSIONS

The present study demonstrates that the level of

cholinesterase is correlated with the damage sever-

ity of the liver cells and may respond to the liver

reserve function of cirrhotic patients. Compared

with the Child-Pugh score and MELD-Na score, se-

rum cholinesterase is less complex and not easily

affected by treatment for decompensated cirrhosis

or other disease. The combination of cholinesterase

with Child-Pugh score or MELD-Na score may be

more subjective and accurate in evaluating the liver

reserve function of cirrhotic patients.

Conflict of interest: none declared

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REFERENCES

1. Fanping M, Xiaojuang Y, Xuemei M, Xiao-Dong G, Bo J, Hanwei Li. Assess-ment of the value of serum cholinesterase as a liver function test for cirrhotic patients. Biomedical reports. Beijing: Pathological Diagnosis and Research Center. 2013 Mar;1(2):265-268. doi: 10.3892/br.2013.60. Epub 2013 Jan 21.

2. Weisinger RS. Laboratory tests in liver disease and approach to the patient with abnormal test. [Book auth.] Goldman L. and Bennett. In Cecil Textbook of Medicine. J(Ceds.) 21st edition. Philadelphia: WB Saunders, 2000, pp. 775-777.

3. Zhou X, Tu ZG. Clinical Biological Chemical and Biological Chemical Inspection 3rd edition. Beijing: People’s Medical Publishing House, 2003, pp. 325-328.

4. Karyone K, Shimatan Y, Kurihara T, Nagao T, Fujita Y, Uesugi M. [Establishing indicators for diagnosis of cholinergic crisis]. Rinsho Byori. 2010 Oct;58(10):972-8. Japanese. PMID: 21077286.

5. Lu Z, Zhong NS. Internal Medicine. 7th edition. Beijing: People’s Medical Publishing House. 2008;453.

6. Zou Z, Xin S, Li B. [Relationship between cholinesterase, prothrombin activity and albumin and the pathology of the liver]. Zhonghua Shi Yan Linchuang Bing Du Xue Za Zhi. 2001 Dec;15(4):349-51. Chinese. PMID: 11986723.

7. Sinha SN, Keresztes-Nagy S, Frankfater A. Studies on the distribution of cholinesterase: Activity in the human and dog heart. Pediatr Res. 2006;10.

8. Kondo M, Hada T, Fukui K, Iwasaki A, Higashino K, Yasukawa K. Enzyme-linked immunosorbertent assay (ELISA) for Aleuria aurantia lectin-reactive serum cholinesterase to differentiate liver cirrhosis and chronic hepatitis. Clin Chim Acta. 1995 Dec 15;243(1-2):1-9. doi: 10.1016/0009-8981(95)60146-0. PMID: 8747509.

9. Ogunkeye OO, Roluga AI. Serum cholinesterase activity helps to distinguish between liver disease and non-liver disease aberration in liver function tests. Pathophysiology. 2006 May;13(2):91-3. doi: 10.1016/j.pathophys.2006.01.002. Epub 2006 Mar 10. PMID: 16530396.

10. McArdle B. The serum cholinesterase in jaundice and diseases of the liver. Quart J Med. 1940;9(1):107. doi:10.1093/QJMF/JQX145.

11. Association of Infectious and Parasitic Epidemiology Branch of Learning Branch of Liver Disease: viral hepatitis prevention and treatment plan. China J Inter Med. 2001:62-8.

12. Wang J, Gao X, Yang Y. Patients with cirrhosis serum cholinesterase clinical research. Chin J Med Guide. 2005:68.

13. Gu YJ, Zhong YB. Cholinesterase determination of evaluation of patients with liver cirrhosis of the liver reserves significance. Chin J Med Guide. 2010:649-50.

14. Prakash R, Mullen KD. Mechanisms, diagnosis and management of hepatic encephalopathy. Nat Rev Gastroenterol Hepatol. 2010 Sep;7(9):515-25. doi: 10.1038/nrgastro.2010.116. Epub 2010 Aug 10. PMID: 20703237.

15. Chromy V, Svachova L, Novosad L. Albumin based or albumin-linked calibration cause a positive bias in serum proteins assayed by the biuret method. Clin Chem Lab Med. 2009;47(1):91-101. doi: 10.1515/CCLM.2009.011. PMID: 19117409.

16. Garg H, Kumar A, Garg V, Sharma P, Sharma BC, Sarina SK. Clinical profile and predictors of mortality in patients of acute-on-chronic liver failure. Dig Liver Dis. 2012 Feb;44(2):166-71. doi: 10.1016/j.dld.2011.08.029. Epub 2011 Oct 5. PMID: 21978580.

17. Vincent D. Transaminases, or nithinecarbamyl transferase, arginase, cholinesterase, etarylesterase. Lyon: Lyon Med 232, 1974, pp. 267-273.