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Original Article

General Medicine Section

The Serum Gamma Glutamyl Transpeptidase - A Non invasive Diagnostic Bio Marker of Chronic Anicteric Non Alcoholic Liver Diseases

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ABSTRACT

Background: The serum gamma glutamyl transpeptidase (GGT) levels rise and return to normal levels later in the chronic anicteric non alcoholic liver diseases than the transaminases levels. So, the estimation of GGT is of some value in monitoring the progress of acute to chronic hepatitis, when the values persist in high levels.

Aims and Objectives: To evaluate the serum GGT levels in patients with chronic anicteric non alcoholic liver diseases and to show that it can be used as a noninvasive diagnostic biomarker for the diagnosis of chronic anicteric non alcoholic liver disorders.

Materials and Methods: This was a case control study, in which 50 cases and 50 controls were selected.The liver function tests with a special reference to the serum level of GGT were measured in the laboratory for both the cases and the controls and the serum GGT levels of the cases were compared with those of the controls. The Chi-square and the Fisher exact tests were used to find the significance of the proportions of the study parameters between the cases and the controls. The Student's t test (two tailed) was used to find the significance mean pattern of the study parameters between the cases and the controls.

Results: The mean serum GGT level was 38.73±11 IU/L in the cases and in the controls, it was 20.42±9 IU/L($p<0.001$). The mean value of serum ALT was 41.37±12.5 vs 16.3±8iu/l($p<0.001$), that of AST was 28.14±8 vs 17.56±8.5iu/l($p<0.05$), that of total bilirubin was 0.9±0.3 vs 0.5±0.2mg/dl and that of serum albumin was 4.17±0.6 vs 4.5±0.75gm/dl, as were seen in the cases and the controls respectively.

Conclusion: The serum gamma glutamyl transpeptidase level was elevated more consistently along with the alanine transaminase level in all types of anicteric nonalcoholic chronic liver diseases. The alanine transminase level has already been proved to be a marker in the diagnosis of chronic anicteric nonalcoholic liver diseases. So, in view of the persistent elevation, along with the high sensitivity, the elevated gamma glutamyl transpeptidase level can also be used as a noninvasive bio marker of chronic anicteric nonalcoholic liver diseases for both diagnostic and therapeutic purposes.

Key Words: Hepatitis, Fatty liver, Serum GGT, Ultrasound abdomen

INTRODUCTION

Chronic liver disease is defined as a series of liver disorders with varying aetiologies and severities, with which hepatic inflammation and necrosis continue for at least 6 months [1]. A variety of biochemical parameters like serum bilirubin, serum proteins, transaminases, gammaglutamyl transpeptidase (GGT), prothrombin time, etc are evaluated to assess the liver cell damage [2]. The hydrolysis of glutathione is mainly done by gamma glutamyl transpeptidase, which is a membrane bound glycoprotein and it also catalyses the transfer of the glutamyl groups from one peptide to another [3, 4]. The GGT activity is considered as a sensitive index of the hepatobiliary dysfunction than alkaline phosphatase, due to its presence in the microsomes and the plasma membranes of hepatocytes [5, 6].

The gamma glutamyl transferase levels rise and return to normal levels later in the liver diseases than the transaminases levels [7]. So, the estimation of GGT is of some value in monitoring the progress of acute to chronic hepatitis, when the values persist in high levels. The gamma glutamyl transferase level may rise more than that of any other enzymes,which may go as high as twelve times the upper limit of the normal and it persists for prolonged periods [8]. Gamma glutamyl transferase is considered as the principal biochemical marker of cholestasis than alkaline phosphatase in children, due its normal activity, which is seen in the young in their growing ages only. When alpa-foetoprotein is negative, the GGT level is very much useful in identifying small tumours of the liver and sometimes it may also be markedly raised in cases of metastatic lesions [7, 9]. The chronic hepatitis which is caused by the hepatitis B and C viruses is associated with high GGT levels, which can be used as a noninvasive diagnostic marker and as a predictor of fibrosis [10, 11].

GGT is normaly present on the tissue membranes of the liver, bile duct, lungs, pancreas, brain, gall bladder, kidneys and the heart muscles. In the diseases of all these organs, we can find significant elevations of the GGT levels [12, 13]. The GGT levels can also be raised in patients who are on a long term treatment with drugs like phenytoin, barbiturates, amiodarone, tomoxifen and steroids and in those who have undergone biliopancreatic surgeries [14].

AIMS AND OBJECTIVES

To evaluate the serum GGT levels in patients with chronic anicteric non alcoholic liver diseases and to show that it can be used as a noninvasive diagnostic biomarker for the diagnosis of chronic anicteric non alcoholic liver diseases.

MATERIALS AND METHODS

This was a case control study which was done on 50 cases who presented to the out patients and in patients departments with vague abdominal pain and easy fatiguability of more than 6 month's duration, without any alcohol intake history and who were taking alcohol of less than 20grams/day [15]. The patients in whom ultrasonological [16] studies proved the presence of chronic liver diseases in the form of fatty liver, chronic hepatitis and cirrhosis were selected, along with 50 healthy volunteers as the controls who had normal ultrasound abdomen reports, who were relatives of the cases, at Srinivasa Hospital, Mukka, Mangalore, India. The patients with renal, pancreas, respiratory, cardiac and neurological diseases, who presented with icterus, who were taking alcohol of more than 20 gm/day, who were on drugs like anti epileptics, amiodarone, tomoxifen and steroids and who had undergone biliopancreatic surgeries were excluded from the study by taking a proper history and by doing a proper exmination and investigations [15].

The investigations such as serum fasting blood sugar, blood routine, urine routine, electrocardiogram, ELISA for the HbsAg, hepatitis C-Igm, ELISA for HIV, the serum ferritin level, the serum copper level, anti nuclear antibodies, lipid profile and liver function tests were done with special reference to the serum GGT levels. The obesity was diagnosed by considering a body mass index (weight in kgs/height in m^2) of more than 30 and the waist circumference [in males >102cm and in females >88cm (NCEP guidelines)] [17]. Diabetes mellitus was diagnosed by considering a fasting blood sugar (FBS) of more than 126mg/dl and a post prandial blood sugar level of more than 200mg/dl according to the American Diabetes Association-7(ADA-7) criteria. A triglycerides level more than 150mg/dl was taken as above normal values (NCEP) [17]. An ALT level of 7-41iu/l, an AST level of 12-38iu/l, a serum albumin level of 3.5-5gm/dl and a serum total bilirubin level of <1mg/dl were taken as normal values [1,2]. The serum GGT levels of the cases were compared with those of the controls. The normal level of GGT was 11-50U/L at 37°C [15,18]. The GGT level in serum was measured by using the Qualigent GGT kit [19].

An ethical clearance was obtained from the ethical committee of Srinivasa Institute of Medical Sciences and Research Centre, Mukka, Mangalore (Ref.No.:SIMSRC/IEC/RP7/13). Written consents were obtained from all the participants after explaining to them in their own language about the study, the methods which would used on them and the risks which were involved.

Statistical Methods: The Chi-square and the Fisher exact tests were used to test the homogeneity of the sex distribution and the Student's t test was used to test the homogeneity of the age distribution. The Chi-square and the Fisher exact tests were used to find the significance of the proportions of the study parameters between the cases and the controls. The Student's 't' test (two tailed) was used to find the significance mean pattern of the study parameters between the cases and the controls.

Statistical Software: The statistical softwares, namely SPSS 11.0 and Systat 8.0 were used for the analysis of the data and Microsoft Word and Excel were used to generate the tables.

RESULTS

This was a case control study in which equal number of cases and contols were included and the results were compared between them. A majority of the study group were in the age group of more than 40 years, in which the cases were 40% and the controls were 54% [Table/Fig-1]. The ages of the cases ranged between 20 and 72 years. The cases included 56% males and 44% females and the controls constituted about 50% males and 50% females [Table/Fig-2]. The main clinical features which were seen were pain in the abdomen with fatty liver in 52% cases (26), liver enlargement in 30% cases (15) and cirrhosis with ascites in 18% cases (9) [Table/Fig-3]. The main causes of the elevated GGT levels which were seen were Diabetes mellitus in 48% cases (24), obesity in 26% cases (13), hypertriglyceridaemia in 8% cases (4), hepatitis which was caused by the hepatitis-B virus in 16% cases (8) and that which was caused by the hepatitis-C virus in 2% cases (1) [Table/Fig-4].

Age in years	Study group(%) N=50	Controls(%) N=50
20-30	14(28)	12(24)
30-40	16(32)	11(22)
>40	20(40)	27(54)

[Table/Fig-1]: Distribution of patients based on age.

Gender	Cases(%)	Controls(%)
Male	28(56)	25(50)
Female	22(44)	25(50)

[Table/Fig-2]: Distribution of study groups based on gender.

Clinical Features	Cases(%)
Liver enlargement	15(30)
Pain abdomen with fatty liver	26(52)
Ascites with cirrhosis	9(18)
	50(100)

[Table/Fig-3]: Distribution of cases based on clinical features.

Causes of High GGT Value	Cases No.(%) n=50
Chronic Hepatitis-B infection	8(16)
Chronic hepatitis-C infection	1(2)
Diabetes mellitus with fatty liver	24(48)
Obesity with fatty liver	13(26)
Hypertriglyceridemia with fatty liver	4(8)

[Table/Fig-4]: Causes For Raised GGT Level.

- Diabetes mellitus is diagnosed by FBS>126mg/dl and PPBS>200mg/dl.
- Obesity is diagnosed by BMI>30.
- Triglycerides level >150mg/dl is taken as high.

The serum GGT level was 38.73±11 IU/L in the cases and in the controls, it was 20.42±9 IU/L,which was statistically significant with a p value of <0.001. The mean value of serum AST

was 28.14±8IU/L vs17.56±8.5IU/L(P-value<0.05), that of ALT was 41.37±12.5IU/L vs16.3±8IU/L(<0.001), that of total bilirubin was 0.9±0.3 vs 0.5±0.2mg/dl and that of serum albumin was 4.17±0.6 vs4.5±0.75gm/dl [Table/Fig-5] in the cases and controls respectively. This clearly showed an increase in the serum GGT levels with the chronicity of the liver disease.

Parameters	Cases (Mean±Sd Value)	Controls (Mean±Sd Value)	P Value
Total Bilirubin(mg/dl)	0.9±0.3	0.5±0.2	<0.05
ALT(iu/l)	41.37±12.5	16.3±8	<0.001
AST(iu/l)	28.14±8	17.56±8.5	<0.05
GGT(iu/l)	38.73±11	20.42±9	<0.001
Serum (gms/dl) Albumin	4.17±0.6	4.5±0.75	0.04

[Table/Fig-5]: Comparison of lab parameters.

- Normal levels of GGT is 11-50iu/l,ALT is 7-41iu/l,AST is 12-38iu/l,serum albumin is 3.5-5.0gm/dl.

DISCUSSION

GGT is elevated to high levels in cases of alcoholic liver diseases than in cases of non alcoholic liver diseases [20]. But GGT is consistently elevated in all the nonalcoholic liver diseases to high levels for prolonged periods of time. So, the estimation of the GGT level is worth, for confirming the diagnosis of chronic anicteric nonalcoholic liver diseases [8]. There are not enough studies which can show that the GGT level is a diagnostic marker of chronic non alcoholic liver diseases.

Serum GGT has been used in the detection of hepato-biliary disease due its sensitive index of chronic liver damage [1]. In my study, about 40% of the cases were in the age group of more than 40 years as compared to the controls. Out of 50 cases, 56% were males and only 44% were females. According to M Irie et al., [19]. nonalcoholic liver diseases are common in the age group of 41.3±18.6 years and in males more than in females.This confirms that chronic non alcoholic liver diseases are common in the middle age group and that they are more common in males than in females [21]. The main clinical features which were seen were fatty liver in 52%, liver enlargement in 30% and cirhosis in 18% of the cases. According to the study of Jeanne M Clark., [22], fatty liver is found in 30 to 40% of the cases and steato hepatic fibrosis is found in 15 to 30% of the chronic non alcoholic liver diseases. This indicates that fatty liver is the most common pathology which is found in chronic non alcoholic liver diseases and that it can progress to cirrhosis in a significant proportion of patients [15, 19, 22]. The causes for the elevated GGT levels were mainly Diabetes mellitus (48%), obesity (26%) and hypertriglyceridaemia (8%). All these cases had fatty liver as the main pathology on ultrasound study. According to the study of Lim J S et al., [23] high GGT levels were found in type 2 diabetes mellitus, hypertriglyceridaemia and in obese patients in significant levels. It is a predictive marker of the progressive damage to the liver in the form of fatty infiltration and cirrhosis. A study which was done by Angulo et al., [21] confirmed that, obesity and diabetes were strong predictive risk factors of fatty liver, severe chronic hepatic fibrosis and cirrhosis of the liver in nonalcoholic chronic liver diseases.This showed that diabetes and obesity were the main causes for the elevation of serum GGT in nonalcoholic chronic liver diseases [15, 23]. Dyslipidaemia in the form of hypertriglyceridaemia, is an important cause of fatty liver [19]. The hepatitis-B and hepatitis-C infections, as causes, were found in 16% (8) and 2% (1) of the cases. Myers and colleagues [24] found that, in patients of chronic hepatitis B, the GGT level can be a significant predictor of hepatic fibrosis due to its consistent elevation in the serum of patients for prolonged periods of time. Giammini et al., [25] found that the chronic hepatitis C patients would suffer a damage to the bile duct in hepatic fibrosis, due to which the GGT level would be significantly raised. This can be considered as noninvasive diagnostic marker in the chronic hepatic fibrosis patients.

This study revealed a significant rise in the serum GGT (p<0.001) levels in patients with anicteric chronic non alcoholic liver diseases. It has been confirmed that the values of AST, ALT, serum albumin and serum GGT varied significantly between the cases with chronic liver diseases and the controls.The serum GGT value was 38.73 ±11 IU/L with a p-value of <0.001 in the cases, which was significantly higher than in the controls. This indicated that, serum GGT is a highly sensitive enzyme which will be raised in chronic anicteric nonalcoholic liver diseases. This study was compared with that of Franzini M-et al., [26]. According to that study, the total GGT was elevated in the nonalcoholic liver disease cases as compared to that in the controls, with values of 39.4 U/L vs. 18.4 U/L respectively, (p < 0.001). According to the study which was done by Giovanni Targher et al., the GGT level in nonalcoholic liver diseases was 38±16iu/L and it was 27±14iu/L in the cases and controls respectively, which was statistically significant, (p<0.001). The GGT level was compared to the alanine trans aminase (ALT) level in the cases, where there was no significant difference between their levels. This meant that the GGT level was equally and significantly elevated as compared to the ALT level. Again, the GGT levels were compared with the AST levels,where the GGT levels were found to be more significantly raised as compared to the AST levels.This was correlated with the findings of the study of Christi A Matteoni et al., [27] where the GGT level was more significantly elevated than the ALT level in chronic non alcoholic liver diseases. According to the study of Giovanni Targher et al., [28] the elevated GGT levels were similar to the ALT levels and they were more elevated than the AST levels in chronic non alcoholic liver diseases. In contrast, in alcoholic liver diseases, it was confirmed that the aspartate transaminase (AST) level was more significantly raised than the GGT and the ALT levels [29]. The elevated GGT level is an important bio marker along with the ALT level in nonalcoholic liver diseases, which is associated with an increased risk of cardiovascular events in diabetic populations [30]. So, estimation of the GGT level can be used as an important and significant marker of chronic anicteric non alcoholic liver diseases.

CONCLUSION

The serum gamma glutamyl transpeptidase level is elevated more consistently along with the alanine transaminase level in all types of Anicteric nonalcoholic chronic liver diseases. The alanine transminase level has been already proved to be as a marker in the diagnosis of chronic anicteric nonalcoholic liver diseases. So, in view of the persistent elevation, along with the high sensitivity, the elevated gamma glutamyl transpeptidase level can also be used as a noninvasive bio marker of chronic anicteric nonalcoholic liver diseases for both diagnostic and therapeutic purposes.

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