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Research Article

THE ROLE OF TRADITIONAL BIOMARKERS IN PATIENTS OF ALCOHOL DEPENDENCE – AN EXPLORATIVE STUDY

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A R T I C L E I N F O

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A B S T R A C T

Heavy consumption of alcohol can cause untold misery to the individual, who is usually affected by other physical, psychological and social disabilities as well. To treat people with alcoholism clinicians need tools like biomarkers that can properly assess not only the patient's past and recent drinking activity but also any history of drinking problems in the family that they may have.This study was a hospital based case control study carried out in a tertiary medical institution located in the upper part of Assam, India. AST, ALT, GGT and MCV levels were significantly elevated in patients of alcohol dependence when compared to controls. The significant elevation of ALT and GGT in alcohol withdrawal patients presenting with withdrawal seizures indicate that their elevated levels could be a risk factor for withdrawal seizures.

INTRODUCTION

The problem of alcohol consumption is a major cause of public health concern in many countries of the world today. Heavy consumption of alcohol can cause untold misery to the individual, who is usually affected by other physical, psychological and social disabilities as well. In 1976 Edwards and Gross proposed the existence of alcohol dependence within a syndrome model. Their description was based on the clinical observation that certain heavy drinkers manifested an interrelated clustering of signs and symptoms. [1] It is a cluster of physiological, behavioural and cognitive phenomena in which the use of alcohol takes on a much higher priority for a given individual than other behaviors that once had greater value. A central descriptive characteristic of the dependence syndrome is the desire (often strong, sometimes overpowering) to take alcohol. [2]

To treat people with alcoholism clinicians need tools that can properly assess not only the patient's past and recent drinking activity but also any history of drinking problems in the family that they may have. Biochemical substances in the body that can indicate the presence or progress of a condition, or any genetic predisposition toward it, are called biomarkers. There are two kinds: State Markers and Trait Markers. State markers provide information about recent drinking activity. Trait markers provide information about a person's genetic predisposition toward alcohol dependence.[3]

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The traditional biomarkers of alcohol include Aspartate Aminotransferase, Alanine Aminotransferase, Gamma Glutamyl Transferase and Mean Corpuscular Volume.[4]

Aspartate Aminotransferase (AST) and Alanine

Aminotransferase (ALT): They are often raised in alcoholics, [5, 6] although generally not more than 2-4 times above the upper limit; sensitivity for AST is around 25-60% whereas it is around 15-40% for ALT. Acute alcohol intakes of 3-4 g/kg body weight may lead to moderate transient increases in AST in healthy individuals within 24-48 hours. The AST: ALT ratio of > 1.5 strongly suggests, and a ratio > 2.0 is almost indicative of, alcohol induced damage to the liver. [7]

Serum Gamma-Glutamyltransferase (GGT)*:* It is a membrane bound glycoprotein which catalyses the transfer of the gamma-glutamyl group to other peptides, amino acids and water. Serum gamma-glutamyl transferase (GGT) activity is found to be increased in the serum in hepatobiliary disorders and with heavy consumption of alcohol. [8] Serum levels of GGT are elevated in about 75% of individuals who are alcohol-dependent, [9-11] with a sensitivity of 60-90%. [12-14]The sensitivity is greatest when alcoholics and heavy drinkers are compared to teetotallers and occasional drinkers. [15]

Mean Corpuscular Volume (MCV)*:* It is the average volume of a red blood corpuscle. The MCV is elevated in 50-60% of alcohol dependence patients. In patients with an alcohol related increase in MCV the enlarged RBCs are round and of uniform size whereas in other types of anemia the enlarged RBCs are oval and of variable size. [16, 17] An increased mean corpuscular volume (MCV) follows chronic heavy drinking and correlates with both the amount and frequency of alcohol

ingestion, [18, 19] but it can take at least a month of drinking more than 60 g alcohol daily to raise the MCV above the reference range. [19] It then takes several months of abstinence for MCV to return to normal, [20] so MCV has no role in monitoring abstinence or relapse.The main weakness of MCV is its low sensitivity both in hospital environments and particularly in primary health care, with an overall sensitivity of 40-50%, but its specificity is high (80-90%) and very few teetotallers and social drinkers will have elevated MCV values.[21- 23]

Aim and Objectives

1. To assess and compare levels of AST, ALT, GGT and MCV in patients of Alcohol Dependence with equal number of age and sex matched controls.
2. To assess and compare levels of AST, ALT, GGT and MCV in patients of Uncomplicated Alcohol Withdrawal State with patients of Alcohol Withdrawal State with Convulsions.

MATERIALS AND METHODS

This study was a hospital based case control study carried out in a tertiary medical institution located in the upper part of Assam, India. The study duration was one year (August 2016-July 2017). The study received the ethical approval from the institutional review board. An informed written consent was obtained from every participant and they were free to withdraw their consent at any point of time. The total sample size was 200 (100 cases and 100 controls). The cases were selected from inpatients, admitted in the institution between August 2016 and July 2017, who were diagnosed as Alcohol Dependence Syndrome or Alcohol withdrawal state with or without Delirium Tremens as per ICD-10, who fulfilled the inclusion and exclusion criteria and gave an informed written consent for participating in the study. In patients of Delirium Tremens written consent was taken from one adult family member (spouse/son/daughter) accompanying the patient. It was seen from previous admission registers of the institution that on an average around 100 patients of alcohol dependence were admitted in one year in the last 5 years (2011-2016). Hence the size of the study group (or case group) was taken to be 100. An equal number of age and sex matched people from healthy population were selected as controls, fulfilling the inclusion and exclusion criteria. The control population comprised of adult family members accompanying the patient and staff members working in the same institution. They did not have any history of alcohol intake in their lifetime. Informed written consent was taken from each of the subjects and they were free to withdraw their consent at any point of time.

Inclusion Criteria

Study Group

1. Patients in the age group of 18 to 65 years.
2. Patients of both the sexes.
3. Cases of Alcohol dependence, Alcohol withdrawal state with or without delirium tremens diagnosed as per ICD-10 and confirmed by Consultant, Department of Psychiatry.
4. Patients giving informed written consent for the study.

Control Group

i. Age and sex matched controls from healthy population who do not consume alcohol.
ii. Persons giving informed written consent for the study.

Exclusion Criteria

Study Group

1. Those with co morbid systemic illness.
2. Those with co morbid mental illness.
3. Those with co morbid other substance abuse.

Control Group

1. Those with history of hepatitis.
2. Those with any systemic illness or mental illness.
3. Those with history of any kind of substance abuse

Assessment Tools

- Informed consent form
- The ICD-10 classification of Mental and Behavioural disorders
- Biochemical estimation of AST, ALT and GGT by bio chromatic rate technique
- Estimation of MCV by automated haematology analyzer
- SPSS version 16.0 for statistical analysis of data

Procedure – Inpatients in the age group of 18 -65 years admitted within the time period of August 2016 to July 2017, and diagnosed as Alcohol dependence (or alcohol withdrawal state with or without delirium tremens) as per ICD-10, confirmed by the consultant and fulfilling the inclusion criteria and exclusion criteria were included in study or case group. Every consecutive case admitted in the study period was selected in the study group till the total sample size was reached. An equal sex and age matched control group was selected from normal healthy population who did not consume alcohol. Written informed consent was taken from each participant of both the study and control group. They were free to withdraw their consent at any given point of time. AST, ALT, GGT and MCV were measured from all the participants of both the groups. From case group, blood samples were collected on the very first day of admission for the sake of uniformity. The blood investigations of both the groups were done in the Laboratories of Department of Biochemistry and Pathology of the same institution. Reference intervals for the measured parameters were considered as per the kits used in Laboratory of Department of Biochemistry and Pathology.Analysis of the observed data was done using tests like Chi square test and unpaired sample t-test in SPSS windows version 16.0. The significance threshold for the tests was set at $p<0.05$.

RESULTS

In both the study and control group most people were in the middle age group between 30 and 53 years. In both the study group and the control group 59 were in the age group of 30-41 years and 26 were in the age group of 42-53 years out of the total sample size of 100 each. Chi Square test was applied to look for significant difference between the age distributions of the two groups. The test result showed a p-value of 0.910 which was statistically insignificant. The study group had a mean age of 40.47 whereas the control group had a mean age

of 38.69. Unpaired sample t-test was applied to look for any significant difference between the mean ages of the two groups The test result showed a p value of 0.1425 which denotes that that there was no statistical significant difference between the groups.

Table 1 Distribution of Case and Control on the basis of age

Age (in years)	Case		Control		X^2	DF	p-value
	no	(%)	no	(%)			
18-29	7	7	9	9	0.5357	3	.910
30-41	59	59	59	59			
42-53	26	26	26	26			
54-65	8	8	6	6			

*p-value significant at < 0.05, DF – Degree of Freedom, X^2 – Pearson Coefficient

Table 2 Mean age distribution of case and control

	Case		Control		p-value
Age (in years)	Mean ± S.D	Range	Mean ± S.D	Range	0.1425
	40.47±8.456	20-60	38.69±8.640	22-60	

*p value significant at <0.05

Both study and control group comprised of 98 males and 2 females respectively. On applying Chi Square no significant difference was found in the distribution of participants in both the groups on the basis of gender.

Table 3 Distribution of case and control according to Gender

Gender	Case		Control		X^2	DF	p-value
	no	%	no	%			
Male	98	98	98	98	0.000	1	1.000
Female	2	2	2	2			

*p value significant at <0.05

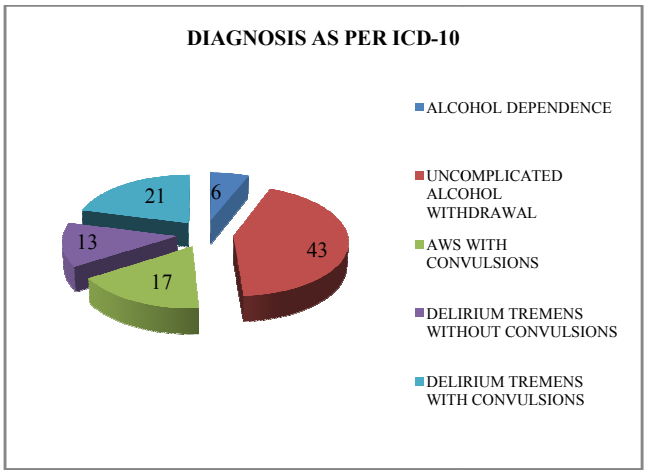

Figure 1 Pie Diagram depicting the diagnosis of cases as per ICD-10

Table 4 Distribution of Case and Control according to Serum AST level

Serum AST (15-37 U/L)	Case		Control		p-value
	no	(%)	no	(%)	
Normal	4	4	93	93	<0.0001*
Elevated	96	96	7	7	
Mean ± SD	178.41 ± 1.35		26.15 ± 6.57		

*p value significant at <0.05

From Table 4, it is seen that the mean AST value in the study group was178.41 with a standard deviation of 1.35 whereas the mean AST value in the control group was only 26.15 with a standard deviation of 6.57. On applying unpaired sample t-test, the p value was found to be <0.0001 which denotes that AST activity wassignificantly higher in the case group than the control group.

Table 5 Distribution of Case and Control according to Serum ALT level

Serum ALT (12-78 U/L)	Case		Control		p-value
	no	(%)	no	(%)	
Normal	63	63	99	99	<0.0001*
Elevated	37	37	1	1	
Mean ± SD	83.65 ± 58.43		47.41 ± 1.45		

*p value significant at <0.05

From Table 5, it is seen that the mean ALT value in the study group was 83.65 with a standard deviation of 58.43 whereas the mean ALT value in the control group was only 47.41 with a standard deviation of 1.45. On applying unpaired sample t-test, the p value was found to be <0.0001 which denotes that ALT activity was significantly higher in the case group than the control group.

Table 6 Distribution of Case and Control according to Serum GGT level

Serum GGT (5-85 U/L)	Case		Control		p-value
	no	(%)	no	(%)	
Normal	5	5	99	99	<0.0001*
Elevated	95	95	1	1	
Mean ± SD	555.33 ± 661.43		33.25 ± 1.93		

*p value significant at <0.05

Table 6 shows that the mean GGT value in the study group was555.33 with a standard deviation of 661.43 whereas the mean GGT value in the control group was only 33.25 with a standard deviation of 1.93. On applying unpaired sample t-test, the p value was found to be <0.0001 which denotes that GGT activity was significantly higher in the case group than the control group.

Table 7 Distribution of Case and Control according to Mean Corpuscular Volume

MCV (79-93.3 fl)	Case		Control		p-value
	no	(%)	no	(%)	
Decreased	7	7	48	48	<0.0001*
Normal	32	32	47	47	
Elevated	61	61	5	5	
Mean ± SD	94.22 ± 8.44		81.00 ± 8.25		

*p value significant at <0.05

Table 7 shows that the Mean MCV in the study group was94.22 with a standard deviation of 8.44 whereas the mean MCV in the control group was81.00 with a standard deviation of 8.25. On applying unpaired sample t-test, the p value was found to be <0.0001 which denotes that there wassignificant difference inMCV between the study and the control group.

Table 8 Comparison of Hepatic Enzymes in Cases of uncomplicated AWS and AWS with convulsions

Hepatic Enzymes	Uncomplicated Alcohol Withdrawal State (AWS)		Alcohol withdrawal State (AWS) with convulsions		p-value
	Mean	SD	Mean	SD	
AST	136.79	101.95	175.44	87.94	0.1752
ALT	76.00	60.39	119.76	61.96	0.0148*
GGT	271.35	249.29	646.29	586.78	0.0009*

*p value significant at <0.05

Table 9 Comparison of Mean Corpuscular Volume in Cases of uncomplicated AWS and AWS with convulsions

	Uncomplicated Alcohol withdrawal state		Alcohol withdrawal State (AWS) with convulsions		p-value
	Mean	SD	Mean	SD	
Mean Corpuscular Volume (79-93.3 fl)	93.281	8.089	93.435	8.909	0.9487

*p value significant at <0.05

Table 8 shows the mean hepatic enzyme levels in cases with uncomplicated alcohol withdrawal state and those with alcohol withdrawal state with convulsions. From the table it is evident that the difference in Mean ALT (p = 0.0148) and Mean GGT (p = 0.0009) between the two groups was statistically significant. On the other hand, there was no significant difference in the Mean AST (p = 0.1752) levels between the two groups.

Table 9 shows the mean MCV levels in cases with uncomplicated alcohol withdrawal state (93.281) and alcohol withdrawal state with convulsions (93.435). On performing unpaired sample t-test, p-value of 0.9487 was obtained which denotes that there was no significant difference in MCV levels between the two groups.

DISCUSSION

Most of the subjects in both the study and control group belonged to the middle age group. The mean age for the study group was 40.47 years whereas the mean age for the control group was 38.69 years. There was no significant difference between the mean ages of the two groups. Majority of subjects in both the study and control groups were males (98% in both groups). There was no significant difference when it came to distribution of subjects in both the groups on the basis of gender. This was an expected finding as an age and sex matched control group was selected for the study sample. Our findings are in accordance with the findings of Pitkänen *et al*. [24] who found that level of alcohol use was significantly higher in men, Jean H. Kim *et al*. [25] who reported that prevalence of alcohol abuse and alcohol dependence were higher among men than women and Juliana Gabrielle Martins-Oliveira *et al*. [26] who found that male adolescents were more likely to develop alcohol dependence in comparison to females.

From the present study it was seen that AST, ALT, GGT and MCV levels were significantly elevated in patients of alcohol dependence when compared to controls. Our findings were in accordance with the findings of Subir Kumar Das *et al*. 2005[27] who reported significant increase in AST, ALT, ALP and GGT activities in alcoholics in comparison to healthy controls, G.Skude *et al*. 1977 [28] who found that, among a total of 182 male chronic alcoholics 73% had increased activity of AST, 50% had increased level of ALT and 69% had increased level of GGT, N. Priya *et al*. [29] who found that AST, ALT and GGT were all raised in alcoholics, which further supported the hepatic damage caused by alcohol, R.J.L Davidson*et al*[30] who reported raised MCV levels in alcoholics in the range 100-108 fl and A.Wul Chanarin *et al*. [31] who found that, among 63 patients regularly drinking more than 80g of ethanol, raised MCV was seen in 89% of them generally unassociated with anemia.

The present study also showed that ALT and GGT were significantly elevated in those patients who presented with alcohol withdrawal seizures compared to those who presented with uncomplicated alcohol withdrawal whereas there was no significant difference in AST and MCV between these two groups of patients. Our findings were in line with the findings of Carrie M. Goodson *et al*. 2014[32] who reported that higher initial ALT and higher initial GGT were seen in patients with incident alcohol withdrawal seizures and D. Mennecier *et al*. 2008 [33] who reported that severe alcohol withdrawal is significantly more associated with direct hospitalization through emergencies and a serum level of ALT greater than 1.5 times the upper limit of normal.

CONCLUSION

The Traditional biomarkers of Alcohol are significantly elevated in patients of alcohol dependence which signify and further validate their efficacy in screening alcoholic patients. The significant elevation of ALT and GGT in alcohol withdrawal patients presenting with withdrawal seizures indicate that their elevated levels could be a risk factor for withdrawal seizures. However further research will be needed to validate our finding which could be a step forward in the early prediction of complicated alcohol withdrawal and their effective treatment. Limitations of the study include its modest sample size, last day of drink being not assessed, cross sectional design of the study and no investigations being done to screen the control population.

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