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Evaluation of Hepatic Enzymes in Uncomplicated Alcohol Withdrawal State and Alcohol Withdrawal State with Convulsions – A Comparative Study

Dr. Abhilekh Das [1], Dr. Lakshimi Borgohain [2]

[1] Post Graduate Trainee (M.D.), Department of Psychiatry, Assam Medical College, Dibrugarh, Assam, India.

[2] M.D., Associate Professor, Department of Psychiatry, Assam Medical College, Dibrugarh, Assam,

Correspondence Author: Dr. Abhilekh Das, Address: Modern Hostel, Assam Medical College and Hospital, Dibrugarh, Assam, India. Pin Code 786002.

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Abstract

Alcoholism is a bio-psychosocial phenomenon par excellence; it is a result of combination of multiple individual and environmental risk factors. Severity of liver damage is often correlated with the amount of alcohol consumption in patients with a history of heavy alcohol abuse. Elevated liver enzymes are an important indicator of the same. The objective of the present study was to measure and compare Hepatic Enzymes in patients with uncomplicated alcohol withdrawal state with those alcohol withdrawal patients presenting with convulsions. The study was carried out in the Department of Psychiatry, Assam Medical College, Dibrugarh over a period of one year (2016-2017). It was a hospital based cross sectional and observational study with a total sample size of 60 in-patients (30 uncomplicated alcohol withdrawal cases and 30 cases of alcohol withdrawal state with convulsions). Cases were diagnosed as per ICD-10 guidelines and SPSS version 16.0 was used for statistical analysis of obtained data setting significance threshold at $p<0.05$. Gamma-Glutamyl Transferase (GGT) and Alanine Aminotransferase (ALT) activity were significantly raised in alcohol withdrawal patients with convulsions compared to patients with uncomplicated alcohol withdrawal state. There was however no significant difference in Aspartate Aminotransferase (AST) and Alkaline Phosphatase (ALP) activity between these two groups of patients. Raised Gamma-Glutamyl Transferase and Alanine Aminotransferase levels could be a risk factor for alcohol withdrawal seizures and may aid in the diagnosis and treatment of such patients.

Keywords: Gamma Glutamyl Transferase, Alanine Aminotransferase, Aspartate Aminotransferase, Alkaline Phosphatase.

Introduction: Consumption of alcohol not only has an impact on the incidence of diseases, injuries and other health conditions, but also on the course of disorders and their outcomes in individuals. Apart from environmental factors Alcohol-related harm is determined by three related dimensions of drinking: the volume of alcohol consumed the pattern of drinking and, on rare occasions, also the quality of alcohol consumed (Rehm et al., 2003a; Rehm, Kanteres & Lachenmeier, 2010; WHO, 2010a).[1]

There are three main direct mechanisms of harm caused by alcohol consumption in an individual (Babor et al., 2003; WHO, 2004b; WHO, 2007). These three mechanisms are:

- Toxic effects on organs and tissues
- Intoxication, leading to impairment of physical coordination, consciousness, cognition, perception, affect or behaviour

- Dependence, whereby the drinker's self-control over his or her drinking behaviour is impaired.[1]

Alcoholism is a bio-psychosocial phenomenon par excellence; it is a result of combination of multiple individual and environmental risk factors. Theories have taken many disparate facts into consideration, from the effects of alcohol policy to the influence of familial and sociocultural environments across cultures and over time. Some ethnic groups have lower rates of alcoholism than others (Asians, Jews and some North American Aboriginals) and the prevalence is higher in males across both age cohorts and ethnicities. Another layer of complexity lies in the fact that alcoholism is a clinically heterogeneous disorder with variable age of onset, drinking patterns, severity and comorbidity with other mental disorders. In general, alcoholics have more than one clinical diagnosis. Common co-morbidities include other drug abuse, antisocial personality disorder, depression and anxiety. [2]

Acute Alcohol Withdrawal [3] - It refers to a group of symptoms of variable clustering and severity occurring on absolute or relative withdrawal of alcohol after repeated and usually prolonged use of alcohol.

Withdrawal symptoms include [3] -

- Minor withdrawal symptoms (can appear 6-8 hours after alcohol has been stopped): Insomnia, fatigue, tremor, mild anxiety, agitation, Nausea and vomiting, headache, excessive Sweating, palpitations, anorexia, depression, Craving for alcohol.
- Psychotic and perceptual disturbances (can appear 12-24 hours after alcohol has stopped): Includes visual, auditory or tactile hallucinations.
- Withdrawal seizures (can appear 12-24 hours after alcohol has stopped): These are generalised tonic clonic seizures.
- Alcohol withdrawal delirium or 'delirium tremens' (can appear any time in first 72 hours upto 1 week after alcohol has been stopped)

Diagnostic Guidelines [4] For Alcohol Withdrawal State

Alcohol withdrawal state is one of the indicators of alcohol dependence syndrome and the latter diagnosis should also be considered. Withdrawal state should be considered as the main diagnosis if it is the reason for referral and severe enough to require medical attention in its own right. Psychological disturbances like anxiety, depression and sleep disorders are also common features of alcohol withdrawal. The patient is likely to report that withdrawal symptoms are relieved by further alcohol use. [4]

Withdrawal symptoms can be also induced by conditioned/learned stimuli in the absence of immediately preceding alcohol use. In such situations alcohol withdrawal state should be diagnosed only if it is warranted in terms of severity. [4]

The diagnosis of alcohol withdrawal state is further specified by using the following five character codes: [4]

F10.30 Uncomplicated

F10.31 With convulsions

Hepatic Enzymes

Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT): They were formerly known as serum glutamate oxaloacetic transaminase (SGOT) and serum glutamic pyruvate transaminase (SGPT) respectively. ALT is mainly localized to the liver but AST is present in variety of tissues like the heart, skeletal muscle, kidney, brain and liver. [5, 6] While AST is present in both the mitochondria and cytosol of hepatocytes, ALT is mainly localized to the cytosol. [5, 7]

Serum Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) are often raised in alcoholics,[8, 9] 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.[11] One study has also shown that AST:ALT ratio is the best of several markers in distinguishing between alcohol- induced and non-alcoholic liver disease.[12]

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. Large amounts of this enzyme are found in the kidneys, pancreas, liver, intestine and prostate. The gene for gamma-glutamyl transferase is on chromosome 22. The levels of Gamma-Glutamyl transpeptidase are higher in neonates and infants up to 1 yr and their levels also increase in elderly subjects after the age of 60. Men seem to have higher values. Children above the age of 4 years have serum values of normal adults. [13, 14] Serum gamma-glutamyl transferase (GGT) activity is found to be increased in the serum in hepatobiliary disorders and with heavy consumption of alcohol. [15] Serum levels of GGT are elevated in about 75% of individuals who are alcohol-dependent, [16, 17, 18] with a sensitivity of 60-90%.[19, 20, 21] The sensitivity is greatest when alcoholics and heavy drinkers are compared to teetotallers and occasional drinkers.[22] However, GGT may not be a very sensitive marker, showing up in only 30–50 percent of excessive drinkers in the general population (Conigrave et al. 2003). Nor is it a very highly specific marker of chronic heavy alcohol use, because other digestive diseases, such as pancreatitis and prostate disease, also can raise GGT levels. [23]

Alkaline phosphatase (ALP): Alkaline phosphatases are a family of zinc metaloenzymes, with a serine at the active centre. Their function is to release inorganic phosphate from various organic orthophosphates and they are present in almost all tissues. In liver, alkaline phosphatase is located in the microvilli of bile canaliculi and also on the sinusoidal surface of hepatocytes. Alkaline phosphatase that is released from liver, bone and kidney are thought to be from the same genetic origin but that which is released from intestine and placenta are believed to be derived from different genes. [14]

Average values of alkaline phosphatase differ with age and they are relatively high in children and adolescents and lower in the middle aged and higher again in elderly people. Males usually have higher values of ALP as compared to the females. [24] Highest levels of this enzyme occur in cholestatic disorders. Elevations occur due to both intrahepatic and extrahepatic obstruction to bile flow and the degree of elevation does not distinguish between the two. Alkaline phosphatase levels are very high in Extrahepatic Biliary Atresia (EHBA). In acute viral hepatitis, alkaline phosphatase is usually in the normal range or it might be moderately increased. Hepatic and bony metastasis can also cause increase the levels of alkaline phosphatase. Decreased levels of alkaline phosphatase occur in hypothyroidism, pernicious anemia, and congenital hypophosphatasia. [6, 14, 25] ALP levels increase with continuous intake of alcohol and monitoring ALP levels is important to identify the etiology and extent of liver disease. [26] The present study makes an effort to assess and compare liver enzymes in uncomplicated alcohol withdrawal with alcohol withdrawal accompanied by convulsions (complicated).

The primary objective of the present study was to measure and compare Hepatic Enzymes in patients with uncomplicated alcohol withdrawal state with those alcohol withdrawal patients presenting with convulsions.

Materials and Methods

The study was carried out in the Department of Psychiatry, Assam Medical College, Dibrugarh over a period of one year (2016-2017). It was a hospital based cross sectional and observational study with a total sample size of 60 patients (30 uncomplicated and 30 complicated cases of alcohol withdrawal state). The study received clearance from the Institutional Ethics Committee.

Selection of study sample: Every consecutive male patient admitted in the Department of Psychiatry within the defined study period, and who were diagnosed as Alcohol withdrawal state as per ICD-10 diagnostic guidelines were included in the study sample till the total sample size was reached. From previous records it was seen that that on an average 30 patients with complicated alcohol withdrawal state were admitted in the institute on a yearly basis for the last 5 years. The sample sizes were made equal for better statistical analysis and to eliminate statistical errors, if any. Before the commencement of the study each of the patients had to give a written consent only after which they were allowed to participate in the study. They were however free to withdraw their consent at any point of time during the study.

Inclusion criteria

- Patients in the age group of 18 to 65 years.
- Patients of only male sex.
- Cases of Alcohol withdrawal state with or without convulsions diagnosed as per ICD-10 diagnostic guidelines
- Patients giving informed written consent for the study.

Exclusion criteria

- Those with co morbid systemic illness.
- Those with co morbid mental illness.
- Those with co morbid other substance abuse.

Assessment tools:

- Informed consent form.
- The ICD-10 Classification of Mental and Behavioural Disorders: Clinical descriptions and diagnostic guidelines.
- Biochemical estimation of hepatic enzymes using bio-chromatic technique.
- SPSS version 16.0 for statistical analysis of obtained data.

Procedure: All patients of male sex in the age group of 18 -65 years, who were admitted in the Drug De-addiction Centre Ward of Department of Psychiatry, AMCH within the time period of August 2016 to July 2017, and diagnosed as Alcohol withdrawal state with or without convulsions as per ICD-10, and fulfilling the inclusion criteria and exclusion criteria were included in study sample. Every consecutive case admitted in the study period was included in the study sample till the total sample size was reached. Written informed consent was taken from each participant of the study sample. They were free to withdraw their consent at any given point of time. Hepatic enzymes were measured from all the participants of the study sample. All blood samples were collected on the very first day of admission for the sake of uniformity. All blood investigations were done in the Laboratory of Department of Biochemistry, Assam Medical College and Hospital, Dibrugarh. Reference Values for the measured blood parameters were used as followed in our Laboratory. Analysis of the observed data was done using unpaired sample t-test in SPSS windows version 16.0. The significance threshold for the tests were set at $p<0.05$.

Results and Discussion

From figure 1 it is seen that out of the total 60 cases of alcohol withdrawal state 30 (50.00%) presented with convulsions whereas the rest 30 (50.00%) were diagnosed as uncomplicated alcohol withdrawal state.

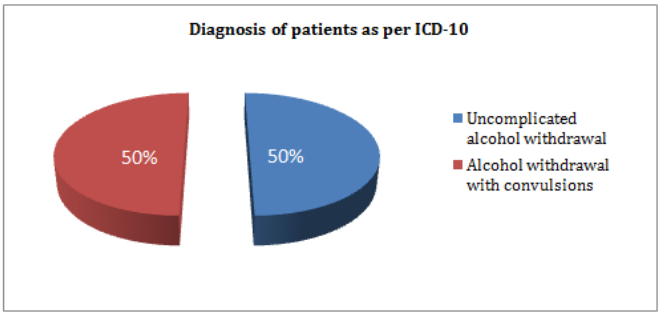

Figure 1: Pie Diagram showing the diagnosis of the cases as per ICD-10.

	Uncomplicated alcohol withdrawal state (UAWS)	Alcohol withdrawal state with convulsions (AWS-C)	p-value
Age (in years)	Mean ± S.D	Mean ± S.D	0.3776*
	39.47±8.58	37.53±8.32	

*p value significant at <0.05

Table 1: Mean age distribution of patients with uncomplicated alcohol withdrawal and alcohol withdrawal patients with convulsions

Table 1 shows the mean age distribution of patients with UAWS and patients with AWS-C. It is seen that the mean age of patients with UAWS is 39.47 whereas the mean age in the complicated group is 37.53. On applying unpaired two sample t test a p-value of 0.3776 is obtained which indicates that there is no significant difference in age between the two groups.

Hepatic Enzymes	Uncomplicated Alcohol Withdrawal State (N_1=30)		Alcohol withdrawal State with convulsions (N_2=30)		p-value
	Mean	SD	Mean	SD	
AST(15-37)	130.72	92.86	164.56	80.94	0.1378
ALT(12-78)	76.42	55.60	116.56	47.86	0.0040*
ALP(46-116)	109.54	36.25	110.23	31.05	0.9372
GGT(5-85)	270.45	180.62	478.60	220.52	0.0002*

*p value significant at <0.05

Table 2: Comparison of Hepatic Enzymes in Cases of uncomplicated AWS and AWS with convulsions

From Table 2 we can clearly see the mean enzyme levels in both the groups. It is seen that the mean AST level in the UAWS group is 130.72 whereas the mean AST in the AWS-C group is 164.56. Similarly the mean ALT, mean ALP and the mean GGT levels in the UAWS group were calculated to be 76.42, 109.54 and 270.45 respectively. On the other hand, the mean ALT, mean ALP and the mean GGT in the AWS-C group were 116.56, 110.23 and 478.60 respectively. On applying unpaired two sample t-test it was seen that there was significant increase in ALT and GGT activity in the complicated withdrawal group compared to the group with uncomplicated alcohol withdrawal whereas there was no significant difference in AST and ALP activity between these two groups of patients.

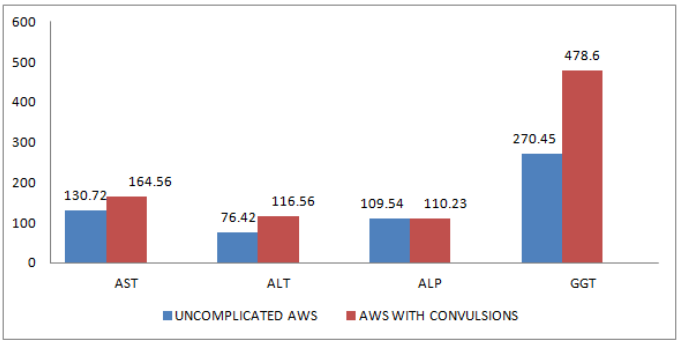

Figure 2: Bar Diagram showing Mean Hepatic Enzyme levels in patients with uncomplicated alcohol withdrawal state and patients of alcohol withdrawal state with convulsions.

In the present study it was seen that the mean AST, ALP and GGT levels in both uncomplicated alcohol withdrawal patients and alcohol withdrawal patients with convulsions were elevated. Mean ALT was elevated in the complicated alcohol withdrawal group but in the uncomplicated group, although it was not elevated beyond the normal range it was still on the higher side. Our findings were in accordance with findings of Alatalo et al. 2008 [86] who reported that serum GGT, AST, ALT were all significantly higher than in alcoholics, Honnamurthy et al. [90] who found that activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and gamma glutamyl transferase (γ-

GT) were significantly higher in alcohol dependence syndrome in comparison to healthy controls, Salma Mahaboob R et al. [68] who reported that GGT, AST and ALT levels were all raised in alcoholic liver disease and N. Priya et al. [95] who found that AST, ALT, ALP and GGT were all raised in alcoholics, which further supported the hepatic damage caused by alcohol. It was also seen in our study that ALT and GGT activity were significantly raised in alcohol withdrawal patients with convulsions compared to those with uncomplicated alcohol withdrawal state. Our finding was in line with the findings of Carrie M. Goodson et al. 2014 [102] 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 [103] 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. On the other hand, there was no significant difference in AST and ALP activities between patients with complicated and uncomplicated alcohol withdrawal states.

Conclusion: Elevated Alanine Transferase and Gamma Glutamyl Transferase activities in alcoholics may be risk factors for alcohol withdrawal seizures. Further research will be however necessary to validate these findings. Limitations of the study included its small sample size, females being not included in the study sample, the cross sectional design of the study and the last day of drink being not assessed which could have led to variation of results.

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