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Original Research Article

Clinicobiochemical and pathological correlation in alcoholic liver disease among Indian patients

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ABSTRACT

Background: Alcohol is one of the leading causes of "preventable" morbidity and mortality worldwide. It is associated with liver damage. A gray area is temporal relation between clinico-biochemical severity and histological changes in liver, neither this issue has been widely studied.
Methods: A hospital based cross sectional clinico-pathological pilot study was undertaken in a tertiary care hospital in West Bengal in patients with a history of alcohol intake who had been admitted in the inpatient department of medicine. Assessment of patients with history of alcohol intake with respect to clinical, biochemical and histopathological examination was performed. The correlation between clinico-biochemical severity and histopathological stages in cases of alcoholic liver disease was evaluated.
Results: There was a significant correlation between clinico-biochemical severity and liver biopsy changes. The severity of histopathological changes of alcoholic liver disease was found to correlate significantly with the severity of abdominal parameters with Pearson correlation cofactor of 0.819.
Conclusions: Both the clinic-biochemical severity and histological changes had no correlation with the duration of alcohol intake in contrast to earlier studies which had demonstrated a definite correlation of alcoholic liver disease (ALD) with both the amount and duration of alcohol intake. Larger studies will be required to substantiate the findings of this study.

Keywords: ALD, Clinical, Biochemical and histopathological

INTRODUCTION

There has been a rapid escalation in alcohol consumption globally over the past decade.[1] Alcohol is one of the two legal substances of abuse in India which is a major risk factor for non-communicable diseases and deaths.[2] Alcohol use continues to be a major public health problem in India. Alcohol use occurs not only in urban but also in remote rural areas in India.[3]

Alcohol is one of the leading causes of "preventable" morbidity and mortality worldwide. The World Health Organization (WHO) report on alcohol and health (2011) states that alcohol abuse is responsible for almost 60 major types of systemic diseases.[4] The harmful use of alcohol causes about 2.5 million deaths each year and a high proportion of this burden is attributed to alcoholic liver disease (ALD). Alcohol not only damages the liver but it is also associated with systemic effects that parallel the severity of liver damage dependent on the alcohol abuse.[5]

Duration and amount of alcohol ingested have been identified as the most important risk factors for the development of a progressive form of alcohol-dependent liver disease. A daily consumption of 60-80 g/d of alcohol for 10 years or longer in men, and 20 g/d in women causes an advanced form of liver disease in <40% of the cases.[5]

The clinical spectrum of ALD ranges from alcoholic fatty liver disease, alcoholic hepatitis, and cirrhosis. 90% of individuals who ingest more than 60 gm/day develop alcoholic fatty liver disease but this is completely reversible with abstinence.[6] But, about 5-15% of them develop alcoholic hepatitis if they continue to drink alcohol. Of these, 50% eventually develop cirrhosis which may complicate into portal hypertension leading to upper gastrointestinal haemorrhage, ascites, splenomegaly and other stigma of chronic liver disease.[7,8] There are more than 200 million alcohol users estimated in India including 1.5 million deaths due to ALD.[9]

Laboratory test results such as liver function tests reveal increased aspartate tansaminase (AST) to alanine transaminase (ALT) ratio in alcoholic hepatitis, altered albumin globulin ratio and increased prothrombin time (PT) in cirrhosis.[6] The histolpathological picture of the liver can help in predicting progression of disease. With the cessation of drinking, steatosis rapidly disappears within weeks, followed by a subsidence of the inflammatory changes. The presence of large mitochondria are indicative of a milder form of alcoholic hepatitis and a lower risk of transformation into cirrhosis whereas polymorphonuclear leukocytosis and perivenular cholestasis foretell a poor prognosis.[8]

Several questions remain still unanswered regarding the relation between alcohol dose and disease risk, including existence of any dose threshold, the influence of sex, and the precise proportion of heavy drinkers who will develop significant liver disease. Another gray area is temporal relation between clinico-biochemical severity and histological changes in liver, neither this issue has been widely studied. This hospital-based study was conducted to find the relationship between clinico-biochemical severity and histologic feature of alcohol induced liver disease, if any.

Aims and objectives

Objectives include: assessment of patients with history of alcohol intake with respect to clinical, biochemical and histopathological examination; and to find out, if any correlation exists between clinico-biochemical severity and histopathological stages in cases of alcoholic liver disease.

METHODS

This hospital based cross sectional clinico-pathological pilot study was undertaken in a tertiary care hospital during the period August 2009 to October 2012 in the department of general medicine at a tertiary care hospital in West Bengal (Nilratan Sarkar Medical College and Hospital).

Patients included in the study had a history of alcohol intake and had been admitted in the inpatient department of medicine. The patients who had contraindications to liver biopsy such as tens ascites, hepatic space occupying lesion or who did not consent to undergo liver biopsy were excluded from the study. Patients who had increased risk of bleeding were also excluded from the study.

After selection of cases, written consent was taken and the patients underwent careful history-taking and physical examinations. The quantity and duration of alcohol consumption were chronicled in the case record form and biochemical evaluation, hemogram, radiological examination, endoscopic examination were conducted. All the cases underwent percutaneous needle biopsy of liver and stained with hematoxylin and eosin (H and E), Mason's trichrome, reticulin, and periodic acid-Schiff (PAS) stains.

28 patients were studied over a period of 15 months. The parameters assessed included history, clinical examination, complete hemogram, blood biochemistry including liver function test, relevant serology, upper gastro-intestinal endoscopy, ultrasound of abdomen and Doppler study of portal vein and histopathological examination of liver (Table 1).

After calculating scores for each patients in: general survey; abdominal examination including ultrasound and endoscopy; biochemistry; a combined score of clinico-biochemical parameter was calculated by adding the score of above mentioned three parameters individually for each patient.

All the twenty-eight patients underwent a percutaneous liver biopsy and examined for histopathological evidence of three broad categories of alcoholic liver disease as follows: fatty liver- centrilobular and perivenular fatty infiltration (presence of intracytoplasmic vacuoles); alcoholic steatohepatitis- ballooning degeneration of hepatocytes, infiltrate of polymorph nuclear leucocytes in hepatic lobules; and cirrhosis of liver- varying degree of fibrosis, perisinusoidal in distribution with regenerating nodules surrounded by thick band of fibrosis, disordered architecture with pseudo lobule formation.

Each of the above categories was assigned a score of one, two and three respectively a child- Pugh-Turcott scoring was done for each patient from all the available data described earlier consisting of ascites, encephalopathy(from history on admission), billirubin, albumin, P time. History of alcohol intake was taken from each patient in the form of duration of alcohol intake including both country liquor. They were assigned score of one, two and three for duration of intake of alcohol for less than 5 years, 5-10 years and more than 10 years respectively.

Analysis

Statistical analysis carried out with SPSS 14.0 (SPSS, USA). Correlation coefficients shown in Table 2. Regression analysis was performed keeping histology of liver as dependent variable and all other parameters like

general survey; abdominal examination including ultrasound of abdomen, Doppler study of portal vein and upper gastrointestinal endoscopy; laboratory parameters including hemoglobin, platelet, transaminases with ratio, bilirubin, albumin, prothrombin time; combination of clinical and biochemical parameters; child-Pugh-Turcott score; alcohol intake as independent variables. By regression analysis, it was aimed to see whether liver histology of an alcoholic patient can be predicted by examining the patient clinically, reports available by common laboratory investigations, radiological tests, endoscopic examination, history of alcoholism and combination of them. Therefore, liver histology was taken as dependent variable.

Table 1: Assessment of the patient.

Feature	Scores assigned
Physical examination	
Icterus	Score of 1 was assigned to each finding if present and 0 if absent
Edema	
Palmar erythema	
Spider naevi	
White nails	
Hair loss	
Gynaecomastia	
Testicular atrophy	
Parotid enlargement	
Dupuytrens contracture	
Abdominal examination along with ultrasound of abdomen to look for dilated portal vein with Doppler study and upper gastrointestinal endoscopy to look for gastroesophageal varix/varices	
Ascites	Each of these features was given a score of one, if they were present or a score of zero, if they were absent.
Prominent superficial abdominal veins flowing away from umbilicas	
Hepatomegaly	
Splenomegaly	
USG of abdomen demonstrating dilated portal vein (diameter more than 12 mm), altered respiratory phasicity in portal vein flow by Doppler study -sign of portal hypertension	
Upper gastrointestinal endoscopy demonstrating gastroesophageal varix/varices indicating portal hypertension	
Biochemistry	
Hemoglobin	Anemia - was given a score of one, zero if absent
Platelet count	Platelet below 1,50,000/cumm - was given a score of one
Ratio of aspartate aminotransferase /alanine aminotransferase (AST/ALT)	A ratio of aspartate aminotransferase /alanine aminotransferase (AST/ALT)- if >1 a score of one given, if >2 a score of two given, if >3 a score of three given
Serum albumin	
Serum bilirubin	
	Raised prothrombin time from control in seconds- if raised by 1-3 sec, a score of one given, if raised by 4-6 sec, a score of two given, if raised by >6 sec, a score of three given
	Low albumin in serum <3.5 gm% - was given a score of one
	Raised billirubin in serum-if 1-2 mg%, a score of one given, if 2-3 mg%, a score of two given, if >3 mg%, a score of three given (parameters taken as in child-Pugh-Turcott score)

RESULTS

The severity of histopathological changes of alcoholic liver disease was found to correlate significantly with the severity of abdominal parameters with Pearson correlation cofactor of 0.819. The correlation of severity between histology and combined score of clinical and biochemical parameters was found to be significant with Pearson correlation cofactor of 0.798. Correlation between histopathology and general survey parameters, biochemical parameters were poor. Correlation between histopathology and duration of intake of alcohol was insignificant.

In regression analysis, the independent variables entered or removed from analysis using the criteria are mentioned in Table 3.

All the factors with p value of univarate and discriminant analysis less than 0.05 entered into the model. Thus, only abdominal parameters were entered into the model and other independent variables were removed from model. The regression analysis demonstrated that only abdominal parameters was able to predict the severity of histological abnormality in a given case of alcoholic liver disease (Tables 2-6).

Table 2: Data collected in this study (scoring as described in data collection).

S. no.	General survey	Abdominal examination	Biochemistry	Combined score	Histopathology	Alcohol intake	CPT score
1	4	4	9	17	3	2	10
2	5	1	6	12	1	3	9
3	0	0	4	4	1	3	6
4	1	1	4	6	1	1	6
5	6	4	8	18	3	3	11
6	0	2	5	7	2	3	6
7	7	3	7	17	3	3	9
8	4	2	9	15	2	2	7
9	0	1	5	6	1	3	7
10	5	5	6	16	3	3	9
11	0	0	3	3	1	2	6
12	5	5	11	21	3	3	11
13	1	0	6	7	3	1	6
14	6	4	8	18	3	3	12
15	0	0	4	4	1	2	5
16	5	5	10	20	3	2	13
17	0	0	8	8	1	2	8
18	5	5	9	19	3	3	10
19	0	0	2	2	1	2	5
20	5	6	8	19	3	3	10
21	1	1	5	7	1	2	6
22	5	3	6	14	2	3	9
23	7	6	10	23	3	3	11
24	4	5	6	15	3	3	8
25	1	1	4	6	3	3	5
26	0	0	3	3	1	2	5
27	7	5	11	23	3	1	11
28	3	2	7	12	2	3	6

Table 3: Correlation between the parameters calculated by using SPSS 14.0.

Parameters	GS	ABS	BIOS	HIS	CPT	ALC	COM
GS							
Pearson correlation	1	0.845	0.767	0.738	0.851	0.299	0.942
Sig.(2-tailed)		0.001	0.001	0.001	0.001	0.123	0.001
N	28	28	28	28	28	28	28
ABS							
Pearson correlation	0.845	1	0.761	0.819	0.835	0.355	0.930
Sig.(2-tailed)	0.001		0.001	0.001	0.001	0.064	0.001

Continued.

Parameters	GS	ABS	BIOS	HIS	CPT	ALC	COM
N	28	28	28	28	28	28	28
BIOS							
Pearson correlation	0.767	0.761	1	0.675	0.840	0.076	0.911
Sig.(2-tailed)	0.001	0.001		0.001	0.001	0.701	0.001
N	28	28	28	28	28	28	28
HIS							
Pearson correlation	0.738	0.819	0.675	1	0.665	0.238	0.798
Sig.(2-tailed)	0.001	0.001	0.001		0.001	0.223	0.001
N	28	28	28	28	28	28	28
CPT							
Pearson correlation	0.851	0.835	0.840	0.665	1	0.234	0.908
Sig.(2-tailed)	0.001	0.001	0.001	0.001		0.231	0.001
N	28	28	28	28	28	28	28
ALC							
Pearson correlation	0.299	0.355	0.076	0.238	0.234	1	0.257
Sig.(2-tailed)	0.123	0.064	0.701	0.223	0.231		0.186
N	28	28	28	28	28	28	28
COM							
Pearson correlation	0.942	0.930	0.911	0.798	0.908	0.257	1
Sig.(2-tailed)	0.001	0.001	0.001	0.001	0.001	0.186	
N	28	28	28	28	28	28	28

Correlation is significant at the 0.01 level (2-tailed, GS: general survey, ABS: abdominal examination score, BIOS: biochemical score, HIS: histological score, CPT: child-Pugh-Turcott score, ALC: alcohol intake score, COM: combination of first three score

Table 4: Criteria for independent variables to enter into regression analysis.

S. no.	Variables entered	Variables removed	Method
1	ABS: abdominal examination score		Stepwise (criteria probability of F to enter ≤0.050, probability of F to remove ≥0.100)

a. Dependent variable: HIS: histology score

Table 5: Coefficients.

Independent variable	Unstandardized coefficients		Standardized coefficients, Beta	t	Sig
	B	Standard error			
Constant	1.271	0.158		8.033	0.000
ABS-abdomial examination score	0.349	0.048	0.819	7.266	0.000

Table 6: Variables excluded from regression analysis.

Independent variables	Beta In	T	Sig	Partial correlation	Collinearity statistics
					Tolerance
GS	0.163[a]	0.764	0.452	0.151	0.285
BIOS	0.124[a]	0.706	0.487	0.140	0.421
CPT	-0.060[a]	-0.290	0.774	-0.058	0.302
ALC	-0.060[a]	-0.491	0.628	-0.098	0.874
COM	0.274[a]	0.893	0.380	0.176	0.135

a. Predictors in model: (constant), ABS; b. dependent variable: HIS; GS: general survey; ABS: abdominal examination score; BIOS: biochemical score; HIS: histological score; CPT: child-Pugh-Turcott score; ALC: alcohol intake score; COM: combination of first three score

DISCUSSION

Alcohol permeates all tissue of body and affects most vital function, because it is a small molecule soluble in both in water and lipids.[10] The liver is the organ most severely affected by alcohol**.** In a prospective study of 280 alcoholic, more than half of those with alcoholic hepatitis and two third of those with cirrhosis died within 48

months.[11] The pattern of drinking in India has undergone a change from occasional and ritualistic as a part of social event to the common purpose of consuming alcohol to get drunk.[12]

Fatty liver is the first manifestation of ALD, can begin to develop within days after heavy drinking and is followed by early fibrosis, which in turn can be associated alcoholic hepatitis, leading to irreversible damage caused by severe fibrosis and subsequently to cirrhosis. Fibrosis is result of necrosis and inflammation is thought to be the underlying mechanism of alcoholic cirrhosis. However cirrhosis may develop without an apparent intermediate stage of alcoholic hepatitis.[13,14] Indeed, independent of necrosis and inflammation, alcohol directly affects lipocytes in the liver (also called stellate, fat storage cell), causing the deposition of collagen, the characteristic protein of fibrous tissue.[15] Long term alcohol consumption transforms lipocytes into collagen producing myofibroblast like cells. In vitro, these cells respond to acetaldehyde with a further increase in collegen and it's mRNA. [16]

Unlike many other hepatotoxins, the likelihood of developing progressive alcohol-induced liver disease or cirrhosis is not completely dose dependent, because it occurs only in a subset of patients. A number of risk factors have been identified that influence the risk of development and progression of liver disease. The relationship between the quantity of alcohol ingested and the development of liver disease is not clearly linear.[17,18] Drinking outside of mealtimes has been reported to increase the risk of ALD by 2.7-fold compared to those who consumed alcohol only at mealtimes.[19] Women have been found to be twice as sensitive to alcohol-mediated hepatotoxicity and may develop more severe alcoholic liver disease at lower doses and shorter duration of alcohol consumption than men. This might be explained by difference in relative amount of gastric alcohol dehydrogenase, a higher proportion of body fat in woman.[20] The presence and extent of protein calorie malnutrition play an important role in determining the outcome of patient with alcoholic liver disease. Mortality increases in direct proportion to the extent to malnutrition. Obesity and excess body fat have been associated with an increased risk of alcoholic liver disease.[21] Polymorphism of genes involved in metabolism of alcohol and in those which regulate endotoxin mediated release of cytokine have been associated with alcoholic liver disease.[22]

The diagnosis of ALD is made by documentation of alcohol excess and evidence of liver disease.[23] No single laboratory marker definitely establishes alcohol as etiology of liver disease. A number of laboratory abnormality have been described. Serum AST is typically elevated to a level of 2-6 times upper limit. Level of AST>500 IU/L or ALT>200 IU/L are uncommon and should suggest another etiology. In about 70% of patient the AST/ALT ratio higher than 2, but this may be of greater value in patient without cirrhosis.[24] Ratio greater than 3 are highly suggestive of alcoholic liver disease.[25] Serum billirubin range from normal to 20-40 mg/dl and serum albumin may be normal or depressed to as low as 1-1.5 g/dl. Most patient are anemic, thrombocytopenic, WBC count usually normal or elevated. Severely ill patient usually have marked prolongation of P-time and serum creatinine value.[26] A liver biopsy is essential for determining the severity of hepatic injury, though liver biopsy is rarely needed to establish the diagnosis.[27]

In this study, among 28 patients: 57% (n=16 had stigmata of CLD such as: ascites (57%), bipedal pitting edema (50%), portal hypertension (50%; and among them, eight were variceal bleeders), loss of body hair (42%), palmar erythema (32%), white nails (25%), gynaecomastia (25%), testicular atrophy (25%), icterus (25%), spider naevi (21%). The remaining 43% patients (n=14) lacked the features of CLD, and 5 of these came in a state of alcohol intoxication. 57% (n=28) had history of alcohol intake for more than ten years of about 150-200 ml daily. 46% patients had high degree of biochemical abnormalities: hypoalbuminemia - (64%), low platelet count (53%), AST>ALT (>3) (17%), raised P time (14%). Histopathologically 50% patients (n=28) had cirrhosis of liver, 14% had alcoholic steatohepatitis and 35% had steatosis respectively.

The Dionysos study demonstrated that incidence of cirrhosis in alcoholic patients was lower but they did not use the gold standard tool of liver biopsy for all patients to assess the severity of ALD.[28] Another study from Mumbai demonstrated that among 327 patients, 41% had cirrhosis and 31% had non-cirrhotic liver disease but this study too did not use liver biopsy as a confirmatory tool in every case.[29] The results of our study corroborate the findings of the earlier studies.

Most of the patients with ALD reached tertiary care in a state where percutaneous liver biopsy was contraindicated (in our institution, transjugular liver biopsy was not possible) or the patient and his relative did not consent to liver biopsy (reflecting psychosocial behavioral pattern). The present study cannot be considered to be an epidemiological representative of the varied presentation of ALD due to the low number of participants and also due to the non–randomized inclusion protocol in this study.

This study had certain limitations: firstly, there was a selection bias because those patients who had contraindications of percutaneous liver biopsy were not included in this study. A transjugular liver biopsy, the best option in those cases, could not be offered. Moreover, sizeable number of the patients with history of alcohol intake who visited the hospital did not consent to liver biopsy, so the numbers of patients included in the study were smaller. Secondly, there was a recall bias regarding the history of amount of alcohol intake. Most patient could remember the duration of alcohol intake better than the amount. Hence, there was a difficulty regarding the calculation of total intake of alcohol. Moreover, different alcoholic beverages have different amount of alcohol by

weight in India, ranging from 22-36 gram/100 ml, which made the calculation further difficult.[11] Earlier studies have shown the most important factor for ALD was both the duration and amount of alcohol intake. The factor of amount of alcohol could not be substantiated by present study. Thirdly, there is no standard, tested, valid protocol to grade the clinico-biochemical severity of ALD, though there are a number of them available for chronic liver disease. Thus, the scoring that was attempted in the present study needs validation by further studies with larger number of patients in future.

The study aimed to assess the severity of ALD in a set-up with limited resources using percutaneous liver biopsy. The present study studied all the patients studied on the basis of three aspects - clinical, biochemical and histopathological.

CONCLUSION

There was a significant correlation between clinico-biochemical severity and liver biopsy changes. Both the clinic-biochemical severity and histological changes had no correlation with the duration of alcohol intake in contrast to earlier studies which had demonstrated a definite correlation of ALD with both the amount and duration of alcohol intake. Larger studies will be required to substantiate the findings of this study so that the severity of alcoholic liver disease can be predicted from clinical and biochemical abnormalities. This may then help avoid liver biopsy to assess severity of alcoholic liver disease and may be useful particularly in settings where liver biopsy may not be feasible.

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