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Research Article

Alteration of cardiovascular autonomic activity in patients of alcoholic liver disease in North-East India: a hospital based study

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ABSTRACT

Background: In the present day world, alcohol consumption is one of the most common and serious public health problems. Alcoholism is a major risk factor for quite a large number of health complications, cardiovascular autonomic dysfunction being one of them. Sudden death in alcoholic liver disease (ALD) patients may be due to undiagnosed and untreated cardiovascular autonomic neuropathy.
Methods: Five standard cardiovascular autonomic function tests were performed to assess the autonomic reactivity in 60 alcoholic liver disease patients at a tertiary care hospital in North-East India and the results were compared with that of 40 ages and sex matched healthy controls.
Results: Out of the 60 ALD patients, 17 (i.e. 28%) have early parasympathetic damage (early PS damage), 25 (i.e., 42%) have definite parasympathetic damage and 18 (i.e. 30%) have a combined type of autonomic damage.
Conclusions: The most affected function in our study is the heart rate response to lying to standing, 40% of the cases showed abnormal 30:15 ratio. Similarly, Blood pressure response to Handgrip test was found to be the least affected one with abnormality percentage of 13%. Present study did not find any pure sympathetic abnormality.

Keywords: Alcoholic liver disease, Cardiovascular autonomic neuropathy, Sympathetic, Parasympathetic

INTRODUCTION

Alcohol has always been an important part of social occasions and rituals even since the ancient times. Today, alcohol consumption is one of the most serious public health problems not just in the developed countries, but in our country as well. A report published by NIMHANS, Bangalore mentioned that one in every 3 Indian males consume alcohol.[1] Alcoholism is considered to be an important risk factor for quite a number of health complications.

It is one of the most common causes of autonomic dysfunction and neuropathy in a significant number of alcoholic populations. Both parasympathetic and sympathetic divisions of the autonomic nervous system (ANS) control the cardiovascular functions in our body; so, disturbance to the ANS leads to severe cardiovascular complications in chronic alcoholics.[2] Sudden death in chronic alcoholics may be attributed to abnormal autonomic reflexes. Documented information regarding autonomic derangements in alcoholics from North- East India is sparse. Considering this fact, the present study aimed to evaluate the cardiovascular autonomic functions in patients with Alcoholic liver disease (ALD) of North East India using the standard Cardiovascular autonomic function tests and compare with that of age and sex matched healthy, non-alcoholic controls.

METHODS

This is a Case-control study. 60 chronic alcoholics, already diagnosed with alcoholic liver disease, who attended various medical outpatient departments of

Silchar Medical College and Hospital, were enrolled in the study. All patients were in the age group of 25 to 55 years. The age of starting of drinking alcohol has decreased in India.[1] Upper age limit has been taken at 55 years to avoid any old age related abnormality of the cardiovascular or neural system. Patients from various parts of Southern Assam and its neighbouring states are referred to Silchar Medical College and Hospital.

The patients were diagnosed as having alcoholic liver disease on the basis of clinical, biochemical, ultrasonographic and upper GI endoscopic findings. All of these patients showed deranged liver function tests for more than six months. Their present liver function tests were done in the Department of Pathology, Silchar Medical College. A group of 40 healthy, non-alcoholic individuals within the same age group as the alcoholics was involved in the study as controls.

Approval from the Institutional Ethical Committee of Silchar Medical College and Hospital was obtained and informed written consent was taken from each case and control volunteering in the study.

Exclusion criteria

- Both chronic alcoholic and non-alcoholics unwilling to give consent to be involved in the study
- Non alcoholics giving history of Hepatitis or Non Alcoholic Fatty Liver Disease (NAFLD)
- Diabetic individuals (to exclude diabetic autonomic neuropathy)
- A person with diagnosis/ symptom of any cardiovascular, respiratory or neural disease
- A person taking medications which might affect the autonomic functions.

A detailed clinical history was taken from each subject. All of the ALD patients gave a strong history of regular consumption of alcohol. Thorough general as well as systemic examinations including neurological examination were performed to exclude any other factor which might affect the autonomic reactivity. Blood glucose was estimated in both alcoholics and their non-alcoholic counterparts to exclude diabetics in either of the groups.

To assess the cardiovascular autonomic functions, all five standard autonomic function tests described by Ewing were done in the Department of Physiology, Silchar Medical College and Hospital.[3]

Immediate heart rate response to standing (30:15 ratio), heart rate variation during deep breathing and heart rate response to Valsalva maneuver test the parasympathetic system while blood pressure response to standing and blood pressure response to sustained hand grip test the sympathetic system. The subjects were asked to take a light breakfast in the morning and the tests were performed preferably at the same time of the day, ie; at around 11:30 AM to avoid any bias. The criteria for Normal, Borderline or Abnormal for each test are shown in Table 1.

Table 1: Cardiovascular autonomic function tests with cut-off limits.[3]

Test	Parameter	Criteria	Category
Heart rate response to Lying to standing	30:15 ratio	>1.04 1.01-1.03 <1.01	Normal Borderline Abnormal
Deep breathing test (DBT)	Delta heart rate(bpm)	>15 11-14 <10	Normal Borderline Abnormal
Valsalva Maneuver	Valsalva ratio (VR)	>1.21 1.11-1.20 <1.10	Normal Borderline Abnormal
BP response to lying to standing	Fall in systolic pressure (mmHg)	<10 11-29 >30	Normal Borderline Abnormal
Handgrip test (HGT)	Change in diastolic pressure (mmHg)	>16 11-15 <10	Normal Borderline Abnormal

Immediate heart rate response to standing (30:15 ratios)

The heart rate was being recorded continuously in the supine position with an Electrocardiogram (BPL). The subject was asked to stand unaided within 3 seconds. The ECG was continuously recorded during the procedure. The point at starting to stand was marked on the ECG.

The characteristic heart rate response was expressed as 30:15 ratios.

It was calculated from the shortest R-R interval at or around the 15th beat and the longest R-R interval at or around the 30th beat after starting to stand up.

Deep breathing test (DBT)

The subject was asked to take slow and deep inspiration followed by slow and deep expiration so that each breathing cycle is of 10 seconds (5 seconds inspiration and 5 second expiration). ECG was continuously recorded throughout the procedure and onset of each inspiration and expiration was marked on the ECG paper. The difference between the maximal and minimal heart rate during inspiration and expiration respectively averaged for 6 cycles (Delta heart rate) was calculated.

Valsalva maneuver

This maneuver was performed in sitting position. The subject was asked to blow into a mouthpiece attached to Sphygmomanometer. The expiratory pressure was maintained at 40 mmHg for 15 seconds (or till the person could bear the strain). At the end of 15 seconds the subject was asked to release the pressure. A continuous ECG was recorded throughout the maneuver. Valsalva Ratio (VR) was calculated from the longest R-R interval during Phase IV and the shortest R-R interval during phase II.

Blood Pressure response to sustained handgrip

The baseline Blood Pressure was taken before the maneuver. A LABOMED handgrip dynamometer was used to determine the maximum voluntary contraction (MVC). The subject was asked to maintain the handgrip at 30% of his MVC for 4 minutes. The blood pressure was recorded at the 1st, 2nd and 4th minute of contraction. The rise in the diastolic blood pressure above the baseline was noted.

Blood Pressure response to standing

This test was conducted after 10 minutes of supine rest. The basal blood pressure was measured and then the subject was asked to attain standing posture within 3 seconds without any support. Blood pressure was measured at 0.5th, 1st, 2nd, 2.5th and 5th minute. The fall in Systolic blood pressure was calculated.

For statistical analysis, we have first calculated the different 'Statistic', say, Mean, Standard Deviation(SD), Standard Error of Mean (SEM) and 95% Confidence Interval (C.I.) of all the parameters. To make comparison between the case and control groups with respect to the different parameters, we determined the p-values by applying Z-test. When our calculated Z-value was greater than 1.96 (ie, $p<0.05$), then we concluded that there is statistically significant difference between the case and the control groups.

RESULTS

The present study has adopted the case-control study design. Out of 75 initially enrolled cases, 6 had diabetes and 9 had been using antihypertensive medication. Therefore, these subjects were excluded from the study. Ultimately 60 alcoholic liver disease patients as cases and 40 healthy non-alcoholic individuals were involved as the control group.

Table 2: Mean distribution of anthropometric and laboratory parameters in experimental and control group.

Parameters	Experimental group (n=60)	Control group (n=40)
Age	40.02±1.26	38.46±2.76
BMI	21.17±2.86	22.65±3.84
SBP	124.13±20.92	123.32±16.40
DBP	78.10±11.02	78.56±11.26
Hb %	12.44±2.75	13.56±2.45
FBS	87.75±7.18	85.17±6.15
PPBS	132.28±7.80	130.75±5.75

*all parameters are expressed as Mean±SD; BMI-Body Mass Index, SBP-Systollic blood pressure, DBP-Diastollic blood pressure, Hb%-Hemoglobin%, FBS-Fasting blood sugar, PPBS- Post prandial blood sugar

The mean distribution of various anthropometric and laboratory parameters of the experimental and control groups is shown in Table2. The patients presented with a wide array of clinical signs and symptoms of ALD and cardiovascular autonomic reactivity. Ultrasonography and Upper GI endoscopy revealed evidences of ALD as presented in Table 3. Among the experimental group, i.e.; among 60 ALD patients, 17 (i.e., 28%) have early parasympathetic damage (early PS damage), 25 (i.e., 42%) have definite parasympathetic damage and 18 (i.e., 30%) have a combined type of autonomic damage, as shown in Figure 1. Overall 72% of our cases showed

autonomic dysfunction. It can be mentioned here, that no sympathetic dysfunction was seen to occur alone. The mean distribution of different parasympathetic and sympathetic function tests among the case and the control groups are summarized and compared in Table 4 and Table 5. The mean for both the groups are within 95% confidence limits and the comparison shows significant result ($p < 0.05$).

Table 3: Presenting features in the experimental group.

Features	Numbers of patients (n)	Percentage (%)
Jaundice	25	41.67
Edema	08	13.33
Haematemesis	30	50.0
Postural Hypotension	18	30.0
Impotence	04	6.67
USG findings		
Free fluid in abdomen	21	35.0
Fatty Liver	24	40.0
Hepatomegaly	37	61.67
Splenomegaly	35	58.33
Cirrhotic changes in Liver	36	60.0
Upper GI endoscopic findings		
Esophageal varices	32	53.33

Table 4: Comparison of parasympathetic function tests between case and control groups.

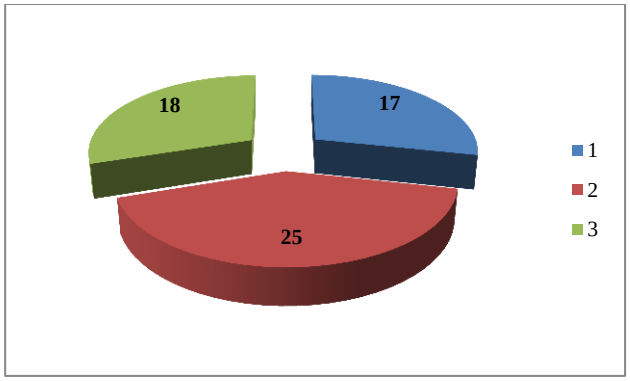
Parameters	Case (n=60)	Control(n=40)	Significance
HR response to standing (30:15 ratio)	0.95 ± 0.15	1.27 ± 0.31	S
Deep Breathing Test	13.53 ± 5.71	18.80 ± 3.16	S
Valsalva Ratio	1.17 ± 0.09	1.25 ± 0.02	S

S- Significant (p-Value <0.05). All values are expressed in Mean±SD.

Table 5: Comparison of sympathetic function tests between case and control groups.

Parameters	Case(n=60)	Control(n=40)	Significance
BP response to standing	13.30±11.0	5.65±2.53	S
Handgrip test	17.0±5.45	19.2±2.56	S

S- Significant (p-Value <0.05). All values are expressed in Mean±SD.



1) Early PS damage; 2) definite PS damage; 3) combined autonomic damage.

Figure 1: Distribution of autonomic neuropathy among 60 chronic alcoholics according to the category of damage.

Out of all the autonomic function tests, the heart rate response to standing has been found to be the most frequently affected test in our study, 38 of the total 60 cases showed abnormal 30:15 ratio. Deep breathing test among the parasympathetic function tests and the handgrip test among the sympathetic function tests were found to be the least affected tests in the respective categories in our study.

DISCUSSION

Autonomic neuropathy is a widely documented complication of diabetes mellitus, and it is nowadays studied also in alcoholics both with liver disease and without liver disease.[4] Autonomic damage is expected in some patients with alcoholic liver disease since autonomic neuropathy, mainly of vagal origin, is seen in chronic alcohol abusers.

In the present study, 43 (i.e. 72%) patients showed autonomic neuropathy. Of these, 25 (i.e. 42%) have definite parasympathetic damage whereas 18 (i.e. 30%) have combined parasympathetic and sympathetic damage. A group of 17 (i.e. 28%) patients showed only a single abnormal test of parasympathetic functions. Since all the procedures in the present study have been performed according to Ewing and Clarke[3], these patients with early parasympathetic damage were classified as not having established autonomic neuropathy.

The results of our study are consistent with similar studies done by Dhillon et al.[5] They showed abnormalities of cardiovascular reflex functions in 60% of their study population.

In another study by Bajaj et al, 80% of the overall study population had evidence of autonomic neuropathy, of which 15% had early parasympathetic damage, 25% had definite parasympathetic damage and 40% had combined autonomic neuropathy.[6] 90% of the alcoholic group and 70% of the non-alcoholic group showed autonomic damage. Such higher frequency of autonomic dysfunction among the alcoholic group in their study may be due to the fact that they have included cirrhotic patients mainly of Child's class B and C.

Singh et al found autonomic dysfunction can occur in patients with liver damage, irrespective of the etiology.[7] They found autonomic dysfunction in 80% alcoholic and 70% of non-alcoholic liver disease patients. Another study by Jain et al observed the magnitude and pattern of autonomic neuropathy in liver cirrhosis where they involved cirrhotic patients irrespective of etiology.[8] They found that 70.9% of the cirrhotic patients had autonomic neuropathy. The minor differences in the results of our study with that of other studies may be attributed to the difference in sample size and to the patient compliance.

CONCLUSION

Man has always enjoyed getting intoxicated but the ill effects of alcohol are many. Due to its silent presence and subtle clinical presentation, Autonomic neuropathy associated with alcoholic liver disease is easily overseen and remain undiagnosed until it becomes fatal. Considering the adverse prognostic implications of CAN, it is recommended that all patients with a diagnosis of alcoholic liver disease should always be tested for CAN to avoid its life threatening complications.

The present study, however, evaluated only the presence of cardiovascular autonomic neuropathy in alcoholic liver disease patients but could not comment whether the actual cause leading to CAN is the liver damage or its etiology, i.e. alcohol. Further study with larger sample size involving liver disease patients of various etiologies can throw more light on this matter.

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