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Original Article

Pattern and Prevalence of Cardiovascular Autonomic Neuropathy (CAN) in Alcoholic Liver Disease Patients in Gauhati Medical College & Hospital, Assam : A Cross-sectional Study

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Abstract

Background and objectives: Alcoholic liver disease is on the rise all over the globe. Cardiovascular autonomic neuropathy is the underlying cause of sudden death in alcoholic liver disease patients. The present study was started with an objective to evaluate the pattern and prevalence of CAN in the alcoholic cirrhosis patients of Assam.

Methods: Heart rate response to lying to standing (30:15 ratio), Deep breathing and Valsalva maneuver were observed to study parasympathetic functions while Blood pressure response to lying to standing and Hand grip test were used for sympathetic functions. For categorization of CAN, two scoring systems were used; the Ewing's criteria and Bellavere's criteria.

Results: The most affected is the heart rate response to lying to standing, 40% of cases showed abnormal 30:15 ratio and Blood pressure response to Handgrip test is the least affected one with abnormality percentage of 13%. Bellavere's criteria scored 76.66% of patients to have CAN but all of the cases (100%) were showed to have CAN when Ewing's criteria were used.

Interpretation and conclusion: CAN develops in alcoholic liver disease which increases the morbidity and mortality in these patients.

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Introduction

Alcoholic liver disease is the most dreaded complication of alcohol abuse. The prevalence of alcoholic liver disease is alarmingly rising all over the world (1), including the North-Eastern part of India, especially in Assam. Alcohol is thought to be one of the commonest factors in today's world to cause autonomic imbalance (2). The patients with alcoholic liver disease show various signs and symptoms of autonomic imbalance at times; some of them complain of light headedness on standing, while others complain of exercise intolerance and some others also complain of erectile dysfunction (3). Unfortunately, many a times, autonomic neuropathy causes sudden death in alcoholic patients who remain undiagnosed (4, 5). Autonomic neuropathy is often an ignored complication of alcoholic liver disease as the symptoms associated with it are usually mild and seem to be not life threatening.

Keeping in mind the risk of development of sudden death in alcoholic liver disease patients, early diagnosis and effective management are very much necessary to improve survival and progress in these patients.

Diagnosis of cardiovascular autonomic neuropathy (CAN) in Alcoholic liver disease (ALD) is done on the basis of Autonomic function tests, which test the autonomic reactivity. The criteria for diagnosis had been put forward by Ewing (6) and Bellavere (7). According to Ewing's criteria, five tests are performed for both parasympathetic and sympathetic components, while Bellavere's criteria are based only on the three tests for parasympathetic components. The autonomic functions in alcoholic liver disease have been a matter of research (5, 8–11), especially in the last three decades or so in many parts of the world but no study regarding cardiovascular autonomic neuropathy in alcoholic liver disease in the North eastern part of India have been reported till now as per the best of our knowledge. Since the number of alcoholic liver disease patients is rising higher and higher with time, this study has been undertaken to assess the pattern and prevalence of cardiovascular autonomic neuropathy in alcoholic liver disease patients admitted in various medical wards in Gauhati Medical College & Hospital in Assam, India.

Objectives

To assess the pattern and prevalence of cardiovascular autonomic neuropathy in alcoholic liver disease patients of Assam.

Hypothesis

Cardiovascular autonomic neuropathy is highly prevalent among chronic alcoholics with alcoholic liver disease.

Materials and Methods

This is a Cross-sectional study, carried out in the Department of Physiology, Gauhati Medical College, Guwahati, Assam. 60 chronic alcoholics, already diagnosed with alcoholic liver disease, who were admitted in various medical wards of Gauhati Medical College & Hospital, were enrolled in the study. Patients from various parts of Assam and its neighbouring states are referred to Gauhati Medical College & Hospital. The patients were diagnosed as having alcoholic liver disease on the basis of clinical, biochemical and ultrasonographic findings. All of these patients showed deranged liver function tests for more than six months and some of them for even more. Their present liver function test reports were obtained from the laboratories.

Approval from the Institutional Ethical Committee was obtained and informed written consent was taken from each patient.

All the patients considered for the study were in the age group of 35 to 55 years to exclude any old age related abnormality of the cardiovascular or neural system. Since no female patient was reported during the study period, all the cases in our study were males. A detailed clinical history was taken from each patient and their attendants. All of them gave a strong history of regular consumption of alcohol for more than ten years. Also, thorough general as well as systemic examinations including neurological examination were performed to exclude any other

factor which might affect the autonomic reactivity of the patients. Blood glucose was estimated in all these patients to exclude diabetic patients. Patients with liver disease of non-alcoholic origin were excluded from the study.

A group of 40 healthy, non-alcoholic, non-diabetic individuals within the same age group as the patients were involved in the study as controls.

To assess the cardiovascular autonomic functions, all five standard autonomic function tests described by Ewing were done. 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 criteria for Normal, Borderline or Abnormal for each test along with their scores are shown in Table II.

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

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

Deep breathing test (DBT)

The patient 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 patient was asked to blow into a mouthpiece attached to Sphygmomanometer. The expiratory pressure was maintained at 40 mmHg for 15 seconds (or till the patient could bear the strain). At the end of 15 seconds the patient 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 patient was asked to maintain the handgrip at 30% of his MVC for 4 minutes. The blood pressure was recorded at the 1^{st}, 2^{nd} and 4^{th} 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 patient was asked to attain standing posture within 3 seconds without any support. Blood pressure was measured at 0.5^{th}, 1^{st}, 2^{nd}, 2.5^{th} and 5^{th} minute. The fall in Systolic blood pressure was calculated.

Scoring and categorization of the patients

1. Ewing's method (6)

Five tests as shown in Table II were used for scoring. CAN was classified into Normal, Early and Severe on the basis of the scoring.

Normal – all tests normal or 1 test Borderline

Early – 1 of the parasympathetic tests Abnormal or 2 Borderline

Definite – 2 heart rate tests Abnormal

Severe – 2 heart rate tests Abnormal + 1 or both BP tests Abnormal

2. Bellavere's method (7)

Only the 3 tests done for parasympathetic system were used for scoring (Table I)

I. Deep breathing test (Delta HR)

II. Valsalva maneuver (Valsalva ratio)

III. Lying to standing test (30:15 ratio)

Scoring was done by adding the scores for each test and CAN was classified as follows :

0 – 1 = no CAN

2 – 3 = early CAN

4 – 6 = definite CAN

Results

Different cardiovascular autonomic function tests mentioned above have been carried out in Gauhati Medical College & Hospital and the different scores have been recorded. Mean, standard deviation etc. were calculated using MS Excel. To make comparison between the case and control groups with respect to the different parameters, p-value was determined by applying Z-test. The value of significance was found to be at $p<0.05$.

Table I shows the significant difference of autonomic function test results between the case and the control groups.

The results of each of the five autonomic function tests on the patients are shown in Table III. 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

TABLE I : Mean distribution of different Autonomic parameters among case and control groups.

Parameters	*Case (n=60)*	*Control (n=40)*	*Value of Z-test*	*Statistical significance*
Heart rate response to standing (30:15 ratio)	0.95±0.15	1.27±0.31	6.07	Significant
Deep breathing test (breaths/min)	13.53±5.71	18.80±3.16	5.92	Significant
Valsalva ratio	1.17±0.09	1.25±0.02	6.64	Significant
Blood pressure response to standing (mmHg)	13.30±11.0	5.65±2.53	5.19	Significant
Hand grip test (mmHg)	17.0±5.45	19.2±2.56	2.71	significant

All values of case and controls are expressed in Mean±SD.

TABLE II : Cardiovascular Autonomic function tests with cut-off limits and scores (6, 7, 14).

Test	*Parameter*	*Criteria*	*Category*	*Score*
Heart rate response to Lying to standing	30:15 ratio	>1.04	Normal	0
		1.01-1.03	Borderline	1
		<1.01	Abnormal	2
Deep breathing test (DBT)	Delta heart rate (bpm)	>15	Normal	0
		11-14	Borderline	1
		<10	Abnormal	2
Valsalva Maneuver	Valsalva ratio (VR)	>1.2	Normal	0
		11.11-1.20	Borderline	1
		<1.10	Abnormal	2
BP response to lying to standing	Fall in systolic pressure (mmHg)	<10	Normal	0
		11-29	Borderline	1
		>30	Abnormal	2
Handgrip test (HGT)	Change in diastolic pressure (mmHg)	>16	Normal	0
		11-15	Borderline	1
		<10	Abnormal	2

TABLE III: Results of each of the Autonomic function tests of the patients (on the basis of criteria mentioned in Table I).

Test	*Parameter*	*Total (n)*	*Normal*	*Borderline*	*Abnormal*	*Ab%*
HR response to lying to standing	30:15 ratio	60	30	6	24	40
Deep breathing test	Delta HR	60	21	22	17	28
Valsalva maneuver	VR	60	27	15	18	30
BP response to lying to standing	Fall in Systolic BP	60	42	3	15	25
Handgrip test	Rise in Diastolic BP	60	49	3	8	13

Ab% = percentage of patients showing abnormal test result.

pressure response to Handgrip test was found to be the least affected one with abnormality percentage of 13%. Our study did not find any pure sympathetic abnormality.

The scoring and categorization of CAN on the basis of Ewing's and Bellavere's criteria are shown in Table IV and Table V respectively. It has been shown that only 46 patients (76.66%) were found to have CAN when we used Bellavere's criteria but all of the 60 patients (100%) were diagnosed as having CAN when we used Ewing's criteria. This finding can be attributed to the fact that Bellavere's criteria consider only the results of the parasympathetic function tests, while Ewing's criteria consider both Sympathetic and parasympathetic function tests.

TABLE IV: Categorization as per Ewing's criteria.

Category	*Number of patients*
Normal	00
Early	17
Definite	25
Severe	18

TABLE V: Categorization as per Bellavere's criteria.

Category	*Number of patients*
Normal (Score 0-1)	14
Early (Score 2-3)	11
Definite (Score 4-5)	35

TABLE VI: LFT profile of the patients.

Parameters	*Patients (n=60)*
Total Bilirubin (mg/dl)	2.31±1.45
SGOT (U/L)	143.07±75.88
SGPT(U/L)	108.40±45.82
Alkaline phosphatase(U/L)	265.70±125.12
Albumin (gm/dl)	2.43±0.63
Hb (%)	8.44±1.03

All values expressed in Mean±SD

The latest Liver function test reports of the patients as collected from the laboratory were studied and various deranged results were found to be present. Table VI shows the LFT profile of the patients.

Discussion

The present study evaluates the pattern and prevalence of CAN among alcoholic liver disease patients of Assam, which is the first of its kind from the North east India as per the best of our knowledge. In contrast to diabetic autonomic neuropathy, which has been investigated in numerous studies, cardiovascular autonomic neuropathy (CAN) in alcoholics has attracted little attention (12). Published figures on the frequency of CAN amongst alcoholics vary between 16 and 77% (12). A study by Bajaj et al (13) on 20 CLD patients showed that 16 out of 20 (80%) had autonomic dysfunction. In their study, 40% had combined parasympathetic and sympathetic damage and 40% had only parasympathetic damage. Another study by Singh et al (11) found autonomic dysfunction can occur in patients with liver damage, irrespective of the etiology. They found autonomic dysfunction in 80% alcoholic and 70% of non-alcoholic liver disease patients.

Khandelwal et al (14) studied the pattern and prevalence of cardiovascular autonomic neuropathy in diabetic patients. They used three different scoring systems for CAN; the Ewing's criteria, Bellavere's criteria and the criteria used at the AFT Lab in AIIMS, New Delhi. They found 53 of total 124 patients had CAN when Bellavere's criteria was used but with

Ewing's criteria 100 patients showed evidence of CAN while 69 could not be categorized. The criteria followed in AFT Lab, AIIMS showed isolated parasympathetic, sympathetic and combined CAN in these patients. The present study is similar to their study. We have used both Ewing's and Bellavere's criteria for the scoring of the alcoholic liver disease patients. We found 46 out of 60 patients had CAN when Bellavere's criteria was used but with Ewing's criteria all the 60 patients were showed to have CAN.

Another study by Jain et al (5) observed the magnitude and pattern of autonomic neuropathy in liver cirrhosis where they involved cirrhotic patients irrespective of etiology. They used only the Bellavere's criteria for scoring the autonomic neuropathy. They found that 70.9% of the cirrhotic patients had autonomic neuropathy.

The patients with Alcoholic liver disease involved in this study were randomly selected from the hospital irrespective of the duration of disease symptoms and severity of the disease, as there are conflicting reports about the association of autonomic neuropathy and severity of liver disease (5). So, we concluded with our findings that CAN may develop in any stage of liver cirrhosis and increases the morbidity and mortality in alcoholic patients. One of the commonest cause of sudden death in alcoholics is occurrence of CAN which may lead to silent myocardial infarction, cardio-respiratory arrest, prolongation of QT interval and arrhythmia (5).

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.

Limitation of the study

This study evaluated only the pattern and prevalence 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, ie. Alcohol. Further study with larger sample size with cirrhotic patients of various etiology can throw more light on this matter.

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