Autonomic Dysfunction in Patients of Alcoholic Liver Cirrhosis

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ABSTRACT

BACKGROUND

Alcohol consumption is prevalent all over world since ages. In men 40-80 g/d of ethanol produces fatty liver; 160 g/day for 10-20 years causes hepatitis or cirrhosis. Only 15 percent of alcoholics develops alcoholic liver disease. Cirrhosis is the final result of hepatic fibrosis and is reversible in the middle stages of development between fibrogenesis and fibrolysis. This disease leads to hemodynamic disorders that can have widespread impacts in the body according to the severity of the cirrhosis. Autonomic dysfunctions have been observed in patients with chronic liver disease. In most of these cases, autonomic dysfunction has been attributed to an alcohol-mediated neuropathy, but other liver-related mechanisms are conceivable as chronic alcoholics with liver damage have higher frequency of neuropathy than those without it.

METHODS

The study group consisted of 100 patients, aged 25 - 60 years of age diagnosed with alcoholic liver cirrhosis on the basis of clinical history and laboratory investigations.

RESULTS

The distribution of age in study population was found to be 41% and 59% in the age group 25-40 and 40-60 years respectively. Among 100 patients recruited for the present study, 71 patients were found to have autonomic dysfunction. The prevalence of autonomic dysfunction was found to be 71% of study population with alcoholic liver cirrhosis. QTc interval was found to be prolonged in cirrhotic patients with autonomic dysfunction as compared to no autonomic dysfunction patients. The abnormality in orthostatic hypotension, HR response to standing and ECG resting tachycardia were found to be statistically significantly associated with Child Pugh Score.

CONCLUSIONS

Autonomic dysfunction becomes more prominent with the severity of alcoholic liver cirrhosis. Autonomic dysfunction increases the morbidity and mortality among patients with alcoholic liver cirrhosis.

KEYWORDS

Alcoholic Cirrhosis, Autonomic Dysfunction, Chronic Liver Disease, Cardiac Autonomic Dysfunction, CLD, Prolonged QTc Interval, Child Pugh Score

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BACKGROUND

Alcohol consumption is prevalent all over the world since ages. Alcohol distributes throughout body tissues and rapidly crosses the blood-brain barrier after its ingestion. Ethanol abuse significantly contributes to damage in a variety of tissues including liver, the central and peripheral nervous systems, and skeletal and cardiac muscle. Continuous consumption of alcohol lead to Liver cirrhosis.[1] In men 40-80 g/d of ethanol produces fatty liver; 160 g/day for 10-20 years causes hepatitis or cirrhosis. Only 15 percent of alcoholics develops alcoholic liver disease.[2] Cirrhosis is the final result of hepatic fibrosis and is reversible in the middle stages of development between fibrogenesis and fibrolysis. This disease leads to hemodynamic disorders that can have widespread impacts in the body according to the severity of the cirrhosis.[3]

The autonomic nervous system (ANS) regulates the activities of cardiac muscle, smooth muscles, endocrine glands and exocrine glands, governing the unconscious body functions, including heart rate, blood pressure, body temperature, gastrointestinal secretion and motility and the metabolic/endocrine responses to stress such as the 'fight or flight' syndrome.[4,5] Most target organs are innervated by neural fibres from both the parasympathetic (vagal) and the sympathetic systems, which act to stimulate organs in opposite ways (antagonistic). For example, vagal stimulation decreases heart rate, while sympathetic stimulation results in increased heart rate.[6, 7] Autonomic dysfunctions have been observed in patients with chronic liver disease.[8] In most of these cases autonomic dysfunction has been attributed to an alcohol-mediated neuropathy, but other liver-related mechanisms are conceivable as chronic alcoholics with liver damage have higher frequency of neuropathy than those without it.[9, 10]

The clinical picture of a patient with CLD presenting with AD is similar for chronic AD of any cause. There are certain clinical features which could be associated with Chronic liver disease like orthostatic hypotension,[11] blurring of vision,[12] fatigue,[13] reduce exercise tolerance,[14] bladder dysfunction,[15] delayed gastric emptying,[16,17] sexual dysfunction[18] and sweating abnormalities.[19]

METHODS

This is a prospective observational study conducted in the Department of Medicine, Chhatrapati Shivaji Subharti Hospital from September 2017 to July 2019. The study group consisted of 100 patients, aged 25-60 years of age diagnosed with alcoholic liver cirrhosis on the basis of clinical history and laboratory investigations. Cases were selected after doing clinical assessment and basic investigations like CBC, LFT, KFT HBsAg. HCV, HbA1c, Lipid profile to rule in alcoholic liver cirrhosis and rule out other causes of liver cirrhosis. Patients were enrolled in the study after obtaining written informed consent from parents and approval from Institutional Ethical Committee. Detailed clinical history including associated symptoms was noted. Detailed systemic examination of patients was done.

Exclusion Criteria

- Patients suffering from co morbidities as Anaemia, hyperthyroidism (as per history), sepsis, hypovolemia, arrhythmias.
- Patients diagnosed with Type II Diabetes Mellitus.
- History of Spinal trauma.
- Drugs Causing prolonged QTc e.g.- Amiodarone, erythromycin, haloperidol, quinidine, amitriptyline, tamoxifen

Clinical Manifestations

Hepatomegaly, Jaundice, Ascites, spider angiomas, fever, Pruritus, variceal bleeding, Hepatic encephalopathy, Splenomegaly, Hepatic fetor, Palmer erythema, Caput medusa.

Laboratory Investigations

(to diagnose alcoholic liver cirrhosis and autonomic dysfunction) Complete Blood Count, Prothrombin Time/ International Normalized Ratio, LFT, KFT, HbA1c (to rule out diabetes and autonomic dysfunction due to diabetes mellitus), ECG (a prolonged QT interval is the most common ECG abnormality seen in patients with liver cirrhosis, USG, HBsAg/HCV, Autonomic Dysfunction Assessment.

For examination, following tests were done-

1. Orthostatic hypotension.
2. Positional orthostatic tachycardia syndrome.
3. Heart Rate Response to Valsalva manoeuvre.
4. Immediate Heart Rate Response to Standing.
5. ECG (heart Rate)- resting tachycardia
6. Urinary symptoms.
7. History of Erectile Dysfunction
8. QTc Interval prolongation-
9. Normal QTc is <430 ms in males and <450 ms in females.
10. Prolonged QTc is >450 ms in males and > 470 ms in females.

Data Recording

Data was collected in structured data collection forms.
All the findings and observations were coded and entered in Excel master sheet.

RESULTS

The distribution of age in study population was found to be 41 and 59% in the age group 25-40 and 40-60 years respectively. Among 100 patients recruited for the present study, 71 patients were found to be present with autonomic dysfunction. Among 100 recruited patients, autonomic

dysfunction parameters were assessed and it was revealed that 71, 72, 69, 67, 61, 61 and 67 patients were found to have abnormality in orthostatic hypotension, HR response to Valsalva manoeuvre, Immediate HR response to standing, ECG resting tachycardia, Urinary symptoms, erectile dysfunction and QTc interval respectively.

The mean ±SD scores of age (years) were found to be 46.47 ± 12.83 and 48.51 ± 10.67 for the patients who were diagnosed with autonomic dysfunction and no autonomic dysfunction respectively. The present study revealed that in relation to age, there was no statistically significant difference found in comparison with presence or absence of autonomic dysfunction during alcoholic liver cirrhosis (p value = 0.464). Child Pugh score was used to assess the prognosis of alcoholic liver cirrhosis. Class A was found to be present in 1 and 2 patients in autonomic dysfunction and no autonomic dysfunction group respectively. Class B was found to be present in 30 and 18 patients in autonomic dysfunction and no autonomic dysfunction group respectively. Class C was found to be present in 42 and 7 patients in autonomic dysfunction and no autonomic dysfunction group respectively. Association of Child Pugh score and autonomic dysfunction was found to be statistically significant (p value <0.01).

In the present study, orthostatic hypotension abnormality was assessed based on prognosis of alcoholic liver cirrhosis by Child Pugh score. It was found that orthostatic hypotension was found to be abnormal in 1, 30 and 41 patients in class A, B and C Child Pugh score respectively. The relationship between abnormality in orthostatic hypotension and Child Pugh score was found to be statistically significant (p value= 0.02). Abnormality in HR response to Valsalva manoeuvre was assessed based on prognosis of alcoholic liver cirrhosis by Child Pugh score. It was found that HR response to Valsalva manoeuvre was found to be abnormal in 1, 32 and 40 patients in class A, B and C Child Pugh score respectively. The relationship between abnormality in HR response to Valsalva manoeuvre and Child Pugh score was not found to be statistically significant (p value= 0.07).

In the present study, abnormality in Immediate HR response to standing was assessed based on prognosis of alcoholic liver cirrhosis by Child Pugh score. It was found that Immediate HR response to standing was found to be abnormal in 0, 29 and 40 patients in class A, B and C Child Pugh score respectively. The relationship between abnormality in Immediate HR response to standing and Child Pugh score was found to be statistically significant (p value= 0.01). The present study depicted the abnormality in ECG resting tachycardia with prognosis of alcoholic liver cirrhosis by Child Pugh score. It was found that ECG resting tachycardia was found to be abnormal in 1, 27 and 39 patients in class A, B and C Child Pugh score respectively. The relationship between abnormality in ECG resting tachycardia and Child Pugh score was found to be statistically significant (p value= 0.01).

In the present study, abnormality in urinary symptoms was evaluated based on prognosis of alcoholic liver cirrhosis by Child Pugh score. It was revealed that urinary symptoms were found to be abnormal in 1, 25 and 36 patients in class A, B and C Child Pugh score respectively. The association between abnormality in urinary symptoms and Child Pugh score was not found to be statistically significant (p value= 0.07). The present study resulted that erectile dysfunction was found to be abnormal in 3, 23 and 38 patients in class A, B and C Child Pugh score respectively. The relationship between abnormality in erectile dysfunction and Child Pugh score was not found to be statistically significant (p value= 0.145). In the present study, it was revealed that QTc were found to be increased among 1, 22 and 44 patients in class A, B and C Child Pugh score respectively. The association between QTc interval and Child Pugh score was found to be statistically significant (p value <0.01).

DISCUSSION

Excessive alcohol consumption is a global healthcare problem with enormous social, economic, and clinical consequences, accounting for 3.3 million deaths in 2012 (World Health Organization 2014). Excessive drinking over decades damages nearly every organ in the body. However, the liver sustains the earliest and the greatest degree of tissue injury from excessive drinking because it is the primary site of ethanol metabolism.[20,21] Heavy ethanol consumption produces a wide spectrum of hepatic lesions, the most characteristic being fatty liver (i.e., steatosis), hepatitis, and fibrosis/ cirrhosis.[22]

Fibrosis and its terminal or late stage, cirrhosis, refer to the deposition of abnormal amounts of extracellular matrix proteins, principally by activated HSCs. Patients initially exhibit active pericellular fibrosis, which may progress to cirrhosis, the late stage of hepatic scarring. The World Health Organization's (2014) Global Status Report on Alcohol and Health estimates that 50 percent of all deaths caused by cirrhosis were attributable to alcohol abuse.[23]

The autonomic nervous system (ANS) regulates the activities of cardiac muscle, smooth muscles, endocrine glands and exocrine glands, governing the unconscious body functions, including heart rate, blood pressure, body temperature, gastrointestinal secretion and motility and the metabolic/endocrine responses to stress such as the 'fight or flight' syndrome.[4] Autonomic dysfunctions have also been observed in patients with chronic liver disease.

In most of these cases autonomic dysfunction has been attributed to an alcohol-mediated neuropathy, but other liver-related mechanisms are conceivable as chronic alcoholics with liver damage have higher frequency of neuropathy than those without it. An interesting hypothesis in cirrhotic patients is that dysautonomia is one of the consequences of the peripheral vasodilation associated with portal hypertension. Peripheral vasodilation stimulates the release of angiotensin and catecholamines which interact with the control of the heart rate variability (HRV).[24] In patients affected by hepatic cirrhosis autonomic dysfunction (AD) is a common finding; usually it is asymptomatic but

may correlate with increased mortality and morbidity before, during and after liver transplantation (LT), due to hemodynamic instability during stressful events like sepsis, gastrointestinal bleeding and reperfusion after transplantation surgery. Hyperdynamic circulation and hepatic dysfunction seem to play a role in the pathogenesis of autonomic dysfunction, even if pathophysiological mechanisms are not completely known.

Evidences previously depicted by studies have discussed about dysautonomia in patients with chronic liver disease. Osztovits et al.[25] had investigated 45 noncirrhotic patients with chronic hepatitis due to hepatitis C virus and 40 healthy controls measuring spontaneous baroreflex sensitivity (BRS) and HRV, a measure of heart rate modulation by the ANS. The authors found that both BRS and HRV were lower in patients than in controls, so corroborating the view that dysautonomia also occurs before the liver becomes cirrhotic.

Stevens et al.[26] have studied a small cohort of patients with primary biliary cirrhosis (PBC) to evaluate if dysautonomia in these subjects is caused by a peripheral nervous system dysfunction in addition to the central dysfunction suggested by the evidence of structural lesions on brain magnetic resonance. The strength of the study includes exclusion of patients with co-morbidities such as Anaemia, hyperthyroidism (as per history), sepsis, hypovolemia, arrhythmias, and patient with spinal trauma and Type II Diabetes mellitus. These exclusions had eliminated the possible confounders but it remains possible that the results could have been affected by residual confounders

The limitation could be that the present study had 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 aetiology, i.e. Alcohol. Further study with larger sample size with cirrhotic patients of various aetiology can throw more light on this matter. Another limitation could be that the present study is a retrospective study, hence it becomes difficult to conclude the causal factors. Further long term cohort studies should be conducted to examine the exact mechanism and cause of autonomic dysfunction in alcoholic liver diseases.

In the present study, the maximum patients with autonomic dysfunction were of age group 40-60 years. Mean age of the study population with autonomic dysfunction was 46.47 years. These results were found to be comparable with the findings presented by Joye Varghese ET al.[27] where the mean age was 39.64 ± 10.6 years for males. Older patients (>40 years) appeared to have more autonomic dysfunction (44 (77.2%) vs. 14 (60.9%)) compared to patients with age <40 years. However, the difference was not statistically significant between age and prevalence of autonomic dysfunction. Females were not included in the present history as on interview they did not present history of alcohol consumption.

The present study documented the prevalence of autonomic dysfunction in 71% of study population. The data are similar to Bajaj ET al.[28] which stated in their study that autonomic function in hepatic cirrhosis with 80% autonomic involvement. In the present study majority of patients belong to Child Pugh score class B and class C. These results were in accordance to the data presented by Bajaj ET al.[28] where only one patient with class A scoring was diagnosed. The association between Child Pugh score and autonomic dysfunction was found to be statistically significant. Hendrickse and Triger[29] reported a strong correlation between the abnormal tests and CTP score ($P < 0.0001$). On the contrary, Gonzalez-Reimer ET al.[30] in their study of 33 alcoholics, 20 of them cirrhotics found a weak correlation between liver function and both autonomic and peripheral neuropathy.

In the present study HR response to Valsalva manoeuvre was the most altered test of autonomic dysfunction followed by orthostatic hypotension and HR response to standing. Barter and Tanner[9] in their study also reported heart rate response to standing as the most sensitive test with high specificity. Impaired cardiac and circulatory (BP) responses to orthostasis in cirrhosis are probably due to blunted baroreflex function. Impaired baroreflex function in cirrhosis can be related to activate renin angiotensin aldosterone system, since administration of canrenone, an aldosterone antagonist, in compensated cirrhotic patients normalizes cardiac response to postural changes.

The present study stated that abnormality in orthostatic hypotension, HR response to standing and ECG resting tachycardia were found to be statistically significantly associated with Child Pugh score. Using standard cardiovascular tests we have found predominately vagal impairment in chronic alcoholic liver disease. Importance of vagal impairment for sodium and fluid retention has been shown in cirrhosis by Hendrickse and Triger et al. Dhillon et al. depicted that Neuromodulation with angiotensin II is proposed as one of the mechanisms inducing parasympathetic dysfunction in cirrhosis and partly correction of vagal dysfunction in cirrhotic patients was achieved by captopril. Hendrickse et al stated in their study that clinical significance of vagal neuropathy detected by standard tests in liver cirrhosis is important. A strong correlation between the number of abnormal test and Child-Pugh score was demonstrated implying that with disease progression cardiovascular autonomic impairment also progress. In multiple regression analysis presence of vagal neuropathy in liver cirrhosis detected by standard autonomic tests is independent predictor of mortality.

Henceforth, considering the limitations of the study we could support the evidence that autonomic dysfunction becomes more prominent with the severity of alcoholic liver cirrhosis. Autonomic dysfunction increases the morbidity and mortality among patients with alcoholic liver cirrhosis. 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. Henceforth, it is recommended that all patients with a diagnosis of alcoholic liver disease should

always be tested for autonomic dysfunction to avoid its life-threatening complications.

CONCLUSIONS

Autonomic dysfunction becomes more prominent with the severity of alcoholic liver cirrhosis. Autonomic dysfunction increases the morbidity and mortality among patients with alcoholic liver cirrhosis.

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