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FREQUENCY OF AUTONOMIC CARDIOVASCULAR DYSFUNCTION IN PATIENTS WITH DECOMPENSATED CHRONIC LIVER DISEASE

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Contribution
AS conceived the idea and designed the study. Data collection and manuscript writing was done by AS, AA, SI, FW, SS, and BR. All the authors contributed equally to the submitted manuscript.

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ABSTRACT

Objective: To determine the frequency of autonomic cardiovascular dysfunction in patents with decompensated cirrhosis.

Methodology: This cross-sectional study was conducted from august 2018 to January 2019 at department of medicine, Abbassi Shaheed hospital. A total of 187 diagnosed patients of decompensated chronic liver disease were consecutively included. Lying and standing BP were taken for orthostatic hypotension while 1 minute ECG was recorded for decrease in HRV during breathing.

Results: Out of 187, 72.7% had autonomic cardiovascular dysfunction.

Conclusion: Almost two thirds of cirrhotic were found to have hemodynamic alterations. Treatment is largely supportive and empiric. Further studies are needed to recognize the burden of autonomic dysfunction.

Keywords: Chronic liver disease, cardiovascular autonomic dysfunction, Heart rate variability (HRV), Cardiac autonomic neuropathy (CAN), Cardiac autonomic reflex tests (CARTS)

INTRODUCTION

Liver cirrhosis is a disease characterized by detoriation in the liver architecture secondary to necrosis, regeneration and deposition of fibrous tissue leading to nodule formation.[1-2] Chronic liver disease has emerged as a serious cause contributing to international burden of liver pathologies. In 2010 cirrhosis was stratified as twenty third responsible factor inflicting 31 million of population, with approximately equal contribution from hepatitis B, hepatitis C and alcohol. Over past twenty years in Europe there is much decline in Alcoholic cirrhosis has been observed. In Asia approximately 50% of the burden of liver illness is secondary to viral hepatitis either B or C.[3] In Pakistan, cirrhosis stands out as a expeditiously accelerating illness, where hepatitis B and C related cases are hospitalized due to decompensated cirrhosis.[4-6] Severity of liver disease is analyzed by using child pugh scoring system which comprises of five variables including bilirubin, albumin, ascities encephalopathy and prothrombin time. For each variable specific values are given on the basis of these values severity of liver disease assessed by dividing into groups like A, B, and C. Each variable has individual points according to their value i.e. 1, 2 and 3 and summation of these lead to identification of severity of disease. Total score range from 5-15, score 5-6 is group A, 7-9 is group B and 10-15 group C, severity is increasing with increasing score.[7]

Autonomic dysfunction is a well-recognized complication of cirrhosis as approximately upto eighty percent of cirrhotic patients with evidence of autonomic neuropathy have so far been observed.[8] As far as the cause of autonomic dysfunction is concerned, hepatotoxic, metabolic and immunological injuries are thought to be the key pathogenic factors.[9-10] Dysautonomia in cirrhosis, is associated with decreased baroreceptor sensitivity to hypotension resulting in impaired Blood pressure and Heart rate responses.[11] Cardiovascular and Autonomic nervous system are closely inter related, an abnormal Autonomic nervous system function in cirrhosis has been reflected in several parameters such as QT prolongation, Heart rate variability (HRV) and arterial pressure changes all as a part of cardiac autonomic neuropathy.[12-13]

The cardiac autonomic reflex tests (CARTS) are considered the gold standard throughout the world for cardiovascular autonomic neuropathy.[5] The panel of test comprises of HR response to deep breathing, standing, valsalva manoeuver, and BP response to standing, these tests are specific, sensitive, easy to perform, safe and straightforward. For definite diagnosis of cardiac autonomic neuropathy(CAN) more than one Heart rate(HR) test and the Orthostatic hypotension OH test required.[14] According to the Subcommittee of the Toronto Consensus Panel statement, defined criteria of CAN and severity for the early diagnosis requires only one abnormal CART result for possible CAN (among the 7 tests : 5 CARTS and HRV test in time and frequency domain), definite CAN should be confirmed by 2 or 3 abnormal tests and severe CAN indicated by development of orthostatic hypotension in combination of abnormal heart rate test.[14]

Autonomic dysfunction is a major contributor to symptomatic drift in disease course and associated with increased mortality. It can be improved by reviewing the drugs used in the management with complication of cirrhosis like beta blocker, diuretics and anti-depressants. Recognition of autonomic dysfunction will be the first step in making a management plan for such patients to reduce morbidity and to some extent mortality.

METHODOLOGY

After approval from the review board, this cross sectional study was conducted from august 2018 to January 2019 at department of Medicine Abbassi shaheed hospital. Sample size was calculated from Rao soft sample size calculator with prevalence of cardiovascular dysfunction in cirrhosis by Bajaj et al.[21] was 85.7% (P=85.7%), Confidence interval (CI=95%) and margin of error (d) was taken as 5% the required sample size was 187 patients. Signed and Informed consent were taken from all patients. Inclusion criteria comprised of patients >18 years of age of either sex, diagnosed with decompensated cirrhosis belonging to child class B and C .Patients with diabetes, h/o alcoholism, any kind of heart disease, respiratory failure; renal failure and malignancy were excluded from the study.

Drugs affecting autonomic function like beta blocker were held four days before testing and diuretics

were held on the day of study. Baseline blood pressure was measured followed by rest of 15 minutes, then to assess for postural hypotension patient was asked to stand, blood pressure was measured immediately and after 3 minutes of standing. If drop in systolic blood pressure was >20mmHg it confirmed the presence of postural hypotension. For heart rate variability during breathing after resting for 5 minutes in a supine position, heart rate was recorded by ECG for 1 min. then patient was instructed to breathe deeply and evenly at six breaths per minute i-e; each inspiration and expiration last for 5 seconds. ECG was recorded during that period. The maximum and minimum heart rate during each breathe cycle was noted for 3 consecutive cycle. The mean difference between maximum and minimum heart rate was calculated. 10-15 beats per min was considered normal, while less than 10 beats per minute was taken as a decrease in heart rate variability. Clinical and demographic characteristics, postural hypotension and heart rate variability during breathing was recorded.

All collected data were entered in SPSS version 16.0. Mean and standard deviation were calculated for age. Frequency and percentages were calculated for gender, age, etiology of CLD, Child Pugh class and autonomic dysfunction.

RESULTS

Table 1: Frequency of CAN with respect to age, gender, etiology, and child pugh classification

Groups	Distribution	CAN
Total (N)	187	136
Age		
18-45	3.7% (7)	0.7% (1)
46-73	73.3% (137)	75.7% (103)
>73	23% (43)	23.5% (32)
Gender		
Male	79.7% (149)	83.1% (113)
Female	20.3% (38)	16.9% (23)
Etiology Of Decompensated CLD		
Hepatitis B	48.7% (91)	47.8% (65)
Hepatitis C	51.3% (96)	52.2% (71)
Child Pugh Class		
B	28.3% (53)	5.1% (7)
C	71.7% (134)	94.9% (129)

Of 187 patients that were enrolled for cardiac autonomic neuropathy, there were 149 males and 38 females with a sex ratio among males vs. female is approximately 4:1. Mean age of patients admitted with decompensated CLD was 55 years with an average age among females and males was same. The cause of cirrhosis was hepatitis B (48.6%) and hepatitis C (51.3%) (Table 1).

Out of 187 patients, 136 patients (72.7%) were found to have cardiac autonomic neuropathy and among 136, 129 patients (94.8%) were of child class C (Table 1). From 136 patients, 97.6% shows sympathetic dysfunction while 63.5% shows parasympathetic dysfunction.

DISCUSSION

Hepatic cirrhosis is a systemic disease with widespread functional consequences affecting almost any organ including cardiovascular[15-16] and neurological system.

Autonomic neuropathy is common in hepatic cirrhosis,[10] previously it was reported that four year mortality in patients with chronic liver disease along with autonomic dysfunction is 30% as compared to 6% in patients with chronic liver disease without autonomic dysfunction.[17] The term cardiac autonomic neuropathy is not specifically used in previous literature of autonomic neuropathy with cirrhosis but most of the authors use same cardiac autonomic reflex test which were used for CAN. Therefore we have discussed cardiac autonomic neuropathy with similar reflex test.

CAN has been a known complication of diabetes[15-16] and alcohol abuse.[18] Previously many authors found that alcoholic patients with liver damage have high frequency of autonomic neuropathy than non-alcoholics.[19,20,25] In our study nonalcoholic and non-diabetic group of patients were selected to demonstrate effect of liver damage on cardiac autonomic nervous system. Surprisingly, we yielded that 72.7% of patients had cardiac autonomic dysfunction which is similar to Bajaj et al. [21] i.e. 70% of the non-alcoholics had autonomic dysfunction. J Perez et al.[22] showed that 60.7% cases in nonalcoholic group had CAN. However study conducted by Gentle et al [23] reveal 57%.Above authors signifies that magnitude of autonomic neuropathy is related to liver damage not alcohol by itself. Jan J et al.[24] in their study concluded that cirrhotic with more than one etiological factor

(Alcohol along with hepatitis B) had higher burden of cardiac autonomic dysfunction as compared to single reason. Similarly Coelho et al.[26] assessed HRV in patients with chronic liver disease with different etiologies which showed significant decline in HRV, which led to the conclusion that severity of hepatopathy is directly proportional to increase in HRV impairment. In other words, CAN can be attributed to the degree of liver damage.

In 2018, another study conducted by Tsiompinads et al. reported 54.9% had CAN the probable cause of lower frequency of CAN in this study was the inclusion of patients with early stage (class A) cirrhosis in majority of study population.[27] A number of authors suggested that CAN is more frequent with B child class and C, like Bajaj reported CAN in patients with child class B cirrhosis of 75% and child class C cirrhosis of 85%,[21] likewise Jain J found CAN in 75.9% patients among patients with child class C cirrhosis.[24] In contrast to this Trevisain F et al.[28] didn't find any diversity in prevalence by dividing patients according to child Pugh classification the study demonstrated 75% belonging to class A or B and 72.7% belonging to class C had documented autonomic neuropathy they did not get any correlation between prevalence of AN and severity of liver disease probably because of small sample size and in their study only 1 patient belonged to child class A.[28] Our study population comprised of patients with decompensated cirrhosis (with child class B and C) showing higher percentages of CAN leading to conclusion that increase in frequency of autonomic dysfunction is related to advancement in liver disease as compared to early liver damage analogous to Bajaj et al.[21], Jain J et al.[24], Peretti et al.[29], and Keresztes et al.[30]

Most of the authors report parasympathetic damage was more common as compared to sympathetic damage like Bajaj et al.[21], Fawi et al.[31], Jain J et al.[24], and J Perez.[22] Surprisingly, our result show sympathetic dysfunction is more 97.6% in contrast to parasympathetic dysfunction which is 63.5%.

Limitation of the study included that we assessed parasympathetic dysfunction by HRV with respiration which is largely dependent on patients' cooperation, and thus not as reproducible as HRV on standing. According to Barter and Tanner HR response to standing is most sensitive test with high specificity.[19] This might be the reason for higher rates of parasympathetic autonomic dysfunction reported in our study.

Secondly to our knowledge, very rare researchers in South Asian subcontinent have evaluated cardiac autonomic neuropathy in cirrhosis of liver till date our study has first time evaluated it in Pakistan but their results could not be generalized because study subjects may not be truly representative of all cirrhotic patients in the community. Thirdly, inclusion of compensated cirrhotic would have further validated the study therefore further studies are required to delineate the factors responsible for the derangement and find remedial measures to improve clinical outcome and quality of life.

CONCLUSION

Almost two thirds of cirrhotic were found to have hemodynamic alterations. Treatment is largely supportive and empiric. Further studies are needed to recognize the burden of autonomic dysfunction and to reduce morbidity and mortality.

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