Original Article

Incidence of Autonomic Neuropathy in Patients with Chronic Liver Disease Due to Chronic Viral Hepatitis

Muhammad Latif, MutiUllah Khan and Azhar Hussain and Muhammad Azhar Shah

Objective: To assess the incidence of Cardiac Autonomic Neuropathy in patients with cirrhosis and its relation with the severity of liver disease.

Methods: Twenty five patients with cirrhosis of liver due to chronic active hepatitis C in various stages and severity of disease were assessed for the presence of cardiac autonomic neuropathy by standard bedside tests of autonomic dysfunction as described by Ewing (Ewing's battery).

Results: Of the patients with class A cirrhosis only one (25%) had early parasympathetic dysfunction. Those belonging to class B cirrhosis, 1 (8%) had early parasympathetic dysfunction, 4 (33%) had definite parasympathetic dysfunction and 2 (17%) had combined sympathetic and parasympathetic dysfunction. Patients with class C cirrhosis 1 (11%) had early parasympathetic dysfunction, 3 (34%) had definite parasympathetic dysfunction and two (22%) had combined parasympathetic and sympathetic dysfunction. None of the patients had isolated sympathetic dysfunction and all with sympathetic dysfunction also had parasympathetic dysfunction. One patient with class B cirrhosis and two with class C cirrhosis had evidence of peripheral neuropathy which was asymptomatic while only three patients with advanced (class C) cirrhosis had symptoms suggestive of autonomic dysfunction like postural dizziness.

Conclusions: Cirrhosis of liver is associated with cardiac autonomic neuropathy which is directly related with severity of illness.

Keywords: cirrhosis, autonomic, neuropathy.

Introduction

Cirrhosis is the end-stage of several disease processes involving the liver. It is associated with several complications that lead to severe morbidity and mortality. Patients with chronic liver disease are known to have disturbed autonomic function since long time. But it is not clear what is the exact prevalence of the abnormality, what is their relation with the severity of disease and what is the clinical impact of these findings. It is also not known how much alcohol itself plays a part in these findings. Recently more interest has been focused on cardiac autonomic neuropathy (CAN) in patients with cirrhosis. It has been found that patients with cirrhosis and CAN respond poorly to stressful conditions like GI bleed and infections thereby leading to poor outcomes1. Patients with cirrhosis and CAN are also known to have increased risk of sudden cardiac death2. Data on this issue is scarce and conflicting and this study was conducted to assess the incidence and pattern of CAN in cirrhotic patients. Simple, non-invasive and reproducible tests are required to check for neuropathy in cirrhotic patients. Ewing and Clarke3in 1982 proposed a battery of five such simple bedside tests (heart rate response to the Valsalva maneuver, deep breathing and standing and the blood pressure response to standing or tilting and to sustained handgrip) to check for autonomic function in diabetic patients and these have also been found to be equally useful for the autonomic dysfunction of cirrhotic patients1,2. A more simple version of these same tests were suggested by O'Brien and colleagues that takes single reading rather than the average of three readings during the Valsalva maneuver were found to be equally useful and more easily and rapidly performed4.Although many investigators have suggested using only three or two or even one of the Ewing's tests to simplify the early diagnosis of CAN, the simplified Ewing's battery remains the gold standard for this purpose5.Few if any local studies were found on this topic while cirrhosis is quite common in our population due the high incidence of chronic hepatitis C virus infection.

Methods

We included twenty five patients with cirrhosis coming to Akhter Saeed Trust Hospital during the period 25-1-2017 to 10-5-2018. All of these patients were suffering from chronic hepatitis C virus infection. The diagnosis was confirmed by detailed history and

Physical examination, lab tests and radiological examination. Hepatitis C virus RNA was detected by quantitative PCR test. Out of these twenty five patients, four were having Child A cirrhosis, twelve with Child B and nine with Child C cirrhosis. Patients with other comorbid conditions like diabetes mellitus, ischemic heart disease and those on drugs that interfere with autonomic function like beta blockers were excluded from the study. Patients on diuretics were also excluded as they may lead to volume contraction and alteration in hemodynamic status of patients. It was also made sure that none of the patients was alcoholic. Specific symptoms in history were noted that point towards symptoms or signs of autonomic dysfunction and detailed physical examination conducted to assess for peripheral neuropathy. Patients' characteristics are summarized in **Table-1.** All these patients were then subjected to battery of five standard tests of autonomic function according to modified Ewing's protocol which are mentioned below.

Tests that reflect cardiac parasympathetic damage; Heart rate response to Valsalva maneuver. During the strain period of valsalva maneuver, the blood pressure falls and heart rate rises. During the release period the blood pressure shoots above resting value and pulse rate slows down. During the test the patient was asked to blow into a manometer and keep a sustained pressure of 40 mmHg for 15 seconds and a continuous ECG is recorded. The result was expressed as the valsalva ratio that is the longest R-R after the maneuver to the shortest R-R interval during the maneuver. Heart-rate (R-R interval) variation during deep breathing. The normal heart rate varies continually and especially during deep breathing, and this depends upon intact parasympathetic system. This is demonstrated by the fact that this normal variation is lost after injection of atropine but is not abolished with administration of propranolol. Patients with autonomic damage due to any cause (like diabetes) have marked reduction in this heart rate variability.

This test was done by asking the patient to breathe deeply at six breaths per minute for one minute while the ECG was being recorded. The maximum and minimum R-R intervals during each cycle were measured and the result was expressed as the average of the difference between the maximum and minimum of the heart rates during each cycle.

Immediate heart rate response to standing, when a patient with intact autonomic nervous system stands up from lying position there is a sharp increase in heart rate which is maximal at about beat 15 followed by a relative bradycardia which is maximum at beat number 30. The test was performed by patient lying quietly on a couch and continuous ECG being recorded. The patient was then asked to stand up unaided and the point of starting to stand was marked on the ECG. The minimum R-R interval at around beat 15 and maximum R-R interval at around beat 30 was noted and the heart rate response expressed as the 30:15 ratio.

Tests reflecting sympathetic damage; Blood pressure response to standing. Upon standing from lying position there is a transient fall in blood pressure due to pooling of blood in the legs but this is rapidly corrected in patients with intact autonomic function. In patients with autonomic dysfunction the blood pressure remains lower than the baseline pressure. The test was performed by checking the blood pressure of the patient while lying quietly on the couch and then one minute after making him to stand up. The postural fall in blood pressure was expressed as the difference between the systolic pressure while lying and the systolic pressure while standing.

Blood pressure response to sustained hand grip. Blood pressure rises sharply during sustained handgrip. In patients with autonomic damage, this rise in BP in blunted. This test is done by asking the patient to apply maximum grip to a modified sphygmomanometer and then maintain the grip at 30% of the maximum for as long as possible. Blood pressure is measured before and at one minute interval during the grip. Result is expressed as the difference between the maximum diastolic pressure during the grip and the average of three readings before the grip. Interpretation of these results was done as suggested by the work of Ewing and Clarke3 **(Table-2).** All these results are interpreted according to work of Ewing and Clarke; with early parasympathetic damage if one of the tests of parasympathetic function is abnormal, definite parasympathetic damage, if two or more of the three tests of parasympathetic function were abnormal; and with combined damage, if one or both the tests of the sympathetic function were abnormal in addition to parasympathetic damage.

Results

In our study, twenty five patients with liver cirrhosis, all due to chronic hepatitis C virus infection, were included. Out of these four belonged to Child's class A, twelve class B and nine to class C. of the patients with class A cirrhosis only one (25%) had early parasympathetic dysfunction. Those belonging to

class B cirrhosis, 1 (8%) had early parasympathetic and parasympathetic dysfunction. Patients with class C cirrhosis 1(11%) had early parasympathetic dysfunction, 3(34%) had definite parasympathetic dysfunction and two(22%) had combined parasympathetic and sympathetic dysfunction. None of the patients had isolated sympathetic dysfunction and all with sympathetic dysfunction also had parasympathetic dysfunction. One patient with class B cirrhosis and two with class C cirrhosis had evidence of peripheral neuropathy which was asymptomatic while only three patients with advanced (class-C) cirrhosis had symptoms suggestive of autonomic dysfunction like postural dizziness. These results are summarized in **Table-3**

Table-1: Patients' characteristics.

Character	Number
Age	44-65 (mean 51) years
Male	08
Female	17
Class A	04
Class B	12
Class C	09
P. Neuropathy	03
Postural symptoms	03

Table-3: Standard interpretation of autonomic function test results.

Group	Normal	Borderline	Abnormal
Tests reflecting parasympathetic function:			
Heart-rate response to Valsalva maneuver (Valsalva ratio)	≥ 1.21	1.11-1.20	=1 10
Heart-rate (R-R interval) variation during deep breathing (maximum-minimumheart rate)	=15 beats/min	11-14 beats/min	=10 beats/min
Immediate heart-rate response to standing (30:15ratio)	=1.04	1.01-1.03	=1-00
Tests reflecting sympathetic function:			
Blood-pressure response to standing (fall in systolic blood pressure)	=10mmHg	11-29mmHg	=30mmHg
Blood-pressure response to sustained handgrip (increase in diastolic blood pressure)	=16mmHg	11-15mmHg	=10mmHg

Table-3: Results of autonomic function testing in cirrhotic patients.

Group	Child class A (n=4)	Child class A (n=4)	Child class A (n=4)
Early parasympathetic damage	1	1	1
Definite parasympathetic damage	0	4	3
Combined damage	0	2	2
Total	1 (25%)	7 (58%)	6 (67%)

Discussion

Autonomic nervous system disorders can occur due to several systemic disorders and can affect any organ system. Commonest causes of chronic autonomic dysfunction include diabetes mellitus, uremia, amyloidosis and several metabolic and toxic conditions including alcoholism.[6] It can also occur due to degenerative diseases of central nervous system like Parkinson's disease and paraneoplastic disorders like that associated with small cell bronchial carcinoma. The fact that patients with chronic liver disease have evidence of autonomic neuropathy is known for long time but initially it was thought that the majority of these findings were associated with alcoholism. Although most of the times these findings are asymptomatic, there has been an increasing. Awareness that these may be associated with increased morbidity and mortality. It has been well established that patients with advanced cirrhosis have increased orocecal transit time (OCTT) and increased gastrointestinal mucosal permeability. These changes favor bacterial translocation from the

Gut and lead to complications like hepatic encephalopathy and spontaneous bacterial peritonitis. Autonomic dysfunction is at least partly responsible for these changes in intestinal structure and function[7,8]. Other implications of altered GI motility include gastroesophageal reflux and reduced oral intake leading to nutritional problems in these patients because of delayed gastric emptying. Hendrickse and Trigerfound that patients with liver cirrhosis who also exhibit impaired autonomic function have fivefold increased risk of mortality, mostly from sepsis and variceal hemorrhage[9]. This increased risk for serious outcomes in patients with advanced cirrhosis who also have GI motility disorder is frequently underestimated and early detection of these complications may be important for prognosis and potential therapeutic intervention[10].While these complications are related with gut associated abnormalities, more interest has been focused on cardiac autonomic neuropathy (CAN) in these patients. Initial reports of CAN in alcoholic cirrhosis came from Barter and Tannerwho found it in at least 36 percent of patients with alcoholism and that most of these patients with CAN were older and had established liver disease. It was not known that the autonomic dysfunction found in these patients was restricted toalcoholic liver disease or to liver disease from any etiology, as all patients included were alcoholics and patients with other etiologies of liver disease were not included.[11] In contrast Gonzalez-Reimerset al found no relation of autonomic neuropathy with liver damage in alcoholics.[12]

Further studies clarified that CAN occurs in patients with advanced liver disease irrespective of the etiology and that the incidence and severity is directly related with the severity of the disease.[1, 13] For example Bajaj et al included equal numbers of patients with alcoholic and non-alcoholic cirrhosis and compared them with equal number of healthy volunteers. They found that incidence of CAN in patients with cirrhosis was directly related with severity of disease and there was no significant difference of incidence in alcoholics and non-alcoholics.[1] Earlier, Dillon et al also showed that patients with cirrhosis have high incidence of autonomic dysfunction irrespective of etiology and the incidence is directly related with advanced stage of the disease.[14] Abdelkaderet al also showed that patients with model for end-stage liver disease (MELD)score of ≥14 had high incidence of autonomic as well as peripheral neuropathy compared with those who have a score <14 and that B_{12} levels were normal in all patients and this was not contributory to the neuropathy.[15]

All these studies showed that patients had either only vagal (parasympathetic) dysfunction alone or combined vagal and sympathetic dysfunction and almost none had isolated sympathetic dysfunction.[6,11] While the five standard autonomic tests have high sensitivity to autonomic dysfunction, 24-hour heart rate variability (HRV) is a powerful noninvasive tool to assess the sympathovagal balance of the heart. Reduced 24-hour heart rate variability is a predictor of sudden cardiac death (SCD) and is probably the most analyzed index in the cardiovascular risk stratification.[16] Patients with cirrhosis of alcoholic or non-alcoholic etiology have evidence of severe abnormalities of sudden cardiac death risk predictors including 24 hours HRV and QTc prolongation.[2,13,14,17] Other studies also showed that patients with advanced cirrhosis awaiting liver transplantation have high incidence of CAN and that this abnormality is significantly improved after transplantation. These studies suggested that evaluation of AN may contribute to a better selection of transplant recipients.[18,19]

In the current study, only one patient with Child A cirrhosis had insignificant impairment of autonomic function while 7 (58%) of twelve patients with Child B and 6 (67%) with Child C cirrhosis had at least some degree of autonomic dysfunction. Few of the patients (only on of twelve with Child B disease and two of the 9 with Child C disease) had evidence of peripheral neuropathy which was asymptomatic, while only three of those with Child C disease and advanced autonomic dysfunction were symptomatic because of these abnormalities.

These results are similar to those with previous studies conducted on this issue. For example the results quoted by Bajaj et al are very similar.[1] Also results from study conducted by Milovanovicet al also show that autonomic dysfunction in patients with cirrhosis is directly related with the severity of the disease and that this dysfunction is reflected in markers of serious ventricular arrhythmias and sudden cardiac death,[2] but this study was conducted on patients with alcoholic Cirrhosis only. However other studies for example conducted by Hendrickse et al and Dillon et al show that these abnormalities occur with similar frequency irrespective of etiology of cirrhosis,[9,14] and study conducted by Abdelkader et al included patients with cirrhosis only from chronic hepatitis C

infection (like our study) and found that autonomic and peripheral neuropathies occur with similar frequency in these patients and that vitamin B12 deficiency plays no role in this finding as commonly considered.[15]

Conclusion

cirrhosis of liver is associated with cardiac autonomic neuropathy which is directly related with severity of illness. The cause of neuropathy is not known but it is associated with worst outcome compared to cirrhotics without neuropathy.

Department of Medicine
Akhter Saeed Trust Hospital
SIMS/Services Hospital, Lahore.

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