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# A study on Autonomic Dysfunction in Patients with Cirrhosis of Liver

KEYWORDS

Autonomic Dysfunction , Hepatic cirrhosis

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**ABSTRACT** This study was conducted to investigate autonomic Dysfunctions in patients with cirrhosis of liver with varied etiology, and to determinethe relationship between severity of liver damage and extentof autonomic function impairment. The present study included 40 patients with Cirrhosis and 40 age and sex matched controls. All the patients and the controls were subjectedto a battery of five standard autonomic function tests. (Valsalva ratio, HR response to deep breathing, Heart rate response to standing, BP response to standing & BP response to sustained hand Grip).Eighty percent (32) of patients with Cirrhosis were foundto have evidence of autonomic Dysfunction. Of these, six (15%)patients had early parasympathetic damage, ten (25%) had definiteparasympathetic damage, and sixteen (40%) had combined (both parasympathetic and sympathetic) damage. Eighteen (90%) ofthe alcoholics and fourteen (70%) of the non-alcoholics had autonomicdysfunction. Autonomic dysfunctionwas significantly abnormal in advanced liver disease comparedwith early liver damage. Light headedness on standingwas the most common symptom of autonomic dysfunction which was more frequently observed in cirrhotics compared withcontrols.Therewas no significant association between symptoms ofautonomic dysfunction and objective evidence of autonomic damageSympathetic dysfunctionalone. was noted in none of our patients.In this study parasympathetic damage was always found in association with an evidence of sympathetic damage.Autonomic dysfunction was found to be proportional to the severity of cirrhosis.

**Background:**

Cirrhosis of the liver leads to anumber of complications, some of which may eventually provefatal. It has been observed that alcoholics with liver damage havehigher frequency of neuropathy than those without it. Thereare reports of association of chronic liver disease with autonomicneuropathy. However; conflicting reports have also appearedcausing much confusion.Patients with cirrhosis and portal hypertension develop hyper dynamic circulation, with increased blood volume andcardiac output, and with a reduced peripheral vascularresistance. This disorder has been related to portal hypertension–induced arterial vasodilatation in the peripheral and splanchnic beds, but other factors may contribute, such asabnormally high levels of circulating vasodilators and false neurotransmitters.[1]Autonomic dysfunction (AD) is seen in both alcohol-related and non-alcohol-related liver disease, and when present is an independent predictor of mortality.[2] It is postulated that patients who were listed for liver transplantation are likely to have a high prevalence of autonomic dysfunction with an associated increase in mortality. On the basis of this observation, preference should be given for early liver transplantation in patients with advanced liver disease and autonomic abnormality. Maheshwari et al hypothesized patients with autonomic neuropathies are more likely to develop hepatic encephalopathy due to a decreased intestinal transit time[3]

Orthostatic hypotension is often the first recognized symptom and typically is the most disabling[4]. Palpitations, nausea, tremulousness, presyncope with light-headedness, visual blurring, tinnitus, and even chest pain andshortness of breath can occur. Orthostatic hypotension may follow and is often associated with postprandial state, alcohol intake, exercise, or temperature-induced worsening of hypotension. Increase in blood pressure in supine position and a loss of diurnal variation in blood pressure may occur later.[5] Micturition and defecation may induce pre syncope. With worsening symptoms, episodes of syncope with complete loss of consciousness after standing may occur.

Gastrointestinal - Constipation, episodic diarrhea, early satiety, increased gastric motility, dysphagia, reduced bowel tone, bowel incontinence, gastroparesis in diabetes mellitus (which can cause food stasis and subsequent vomiting, hyposalivation, and altered sense of taste[6]

**Aim of the Study**

**1.** To investigate autonomic Dysfunctions inpatients with cirrhosis of varied etiology (in both alcoholics and non-alcoholics)

**2.** To analyze characteristics of patients who develop autonomic dysfunction

**3.** To determine the relationship between severity of liver damage and extent of autonomic function impairment.

**Materials and Methods:**

**Study Design** : Case control study

The study was conducted in Government General Hospital, Chennai, during the period of April 2006to March2007. and protocol of the study was submitted to the ethical committee of the hospital and the approval was obtained. The study was carried out on 40 patients with Cirrhosis (20 alcoholics - 80g of alcohol per day for 10 year and 20 non-alcoholics) and 40 age and sex matched controls in the Department of Medical Gastroenterology, Madras Medical College, Chennai.

The diagnosis of Cirrhosis was made, on history, clinical examination, laboratory parameters, ultra sonographic findings, and the presence of oesophageal varices. The controls were healthy volunteers with no history of alcohol consumption and normal clinical and biochemical parameters. A detailed clinical history with special reference to symptoms of autonomic disturbance was taken from each subject and a thorough physical examination including neurological assessmentwas carried out.

A careful and complete history, as well as clinical examination as per proforma was performed. Following investigations were done for all patients. Complete blood counts, Bleeding time, Clotting time, Prothrombin time, Urinalysis, Stool examination for parasite and occult blood, Blood Sugar, Urea, Electrolytes, Creatinine, Serum Bilirubin SGOT, SGPT, Alkaline Phosphatase, Total protein, Albumin, Globulin, Ascitic fluid protein, albumin, SAAG, amylase, cell count and cytology, viral markers like HBsAg, AntiHCVAb, serum Cerulopalsmin in selected cases, Chest X ray, USG abdomen, Doppler study of portal venous system (in selected cases), and UGI endoscopy. Amount of ethanol intake, frequency and type were noted and so also

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about other drug usage. All the patients and the controls were subjectedto a battery of five standard autonomic function tests as detailedbelow.

Statistical analysis was carried out using SPSS windows 11.5 version.

**INCLUSION CRITERIA**

Symptoms and signs of parenchymal liver disease in the form of jaundice, swelling of legs and abdomen, unexplained asthenia, fever, anorexia, altered sleep pattern, bleeding tendency, spider nevi , palmar erythema, dupytren'scontracture, gynacomastiaand astrexis. High SAAG ascites and or evidence of portal hypertension by clinical,endoscopic, Doppler ultra sound examination, and liver biopsies were performed whenever feasible.

**EXCLUSION CRITERIA**

Patients diagnosed as acute viral hepatitis,Liversecondarieswith known or unknown primaries, Obstructive jaundice as evidenced by ultrasound, or ERCP, Cases diagnosed to have Budd-Chiari syndrome, VOD, EHPVO or non cirrhotic portal hypertension.,Cases where EHPVO or NCPF could not ruled out with certain after exhaustive testing, Subjects who were known diabetes mellitus, ischemic heart disease and other medicalconditions, and drugs thatcauses autonomic disturbance were excluded fromthe study.

**Tests reflecting sympathetic damage**

Blood pressure response to standing

This test measured the subject's blood pressure with asphygmomanometer while he was lying quietly and one minute afterhe was made to stand up. The postural fall in blood pressurewas taken as the difference between the systolic pressure lyingand the systolic blood pressure standing. The test was repeatedthree times and the mean was calculated.

**Blood pressure response to sustained hand grip**

The blood pressure of the patient was taken three times beforethe manoeuvre. A modified sphygmomanometer was used for sustainedhandgrip manoeuvre. The patient was asked to grip the inflatablerubber bag and apply maximum voluntary pressure possible. Areading from the attached mercury manometer was taken duringmaximum voluntary contraction.

Thereafter, the patient was askedto maintain 30% of maximum voluntary contraction for as longas possible up to five minutes. Blood pressure was measuredat one minute intervals during the handgrip. The result wasexpressed as the difference between the highest diastolic bloodpressure during the handgrip exercise and the mean of the threediastolic blood pressure readings before the handgrip began.

**Tests reflecting cardiac parasympathetic damage**

Heart rate response to Valsalvamanoeuvre. The subject was seated quietly and then asked to blow into amouthpiece attached to a manometer, holding it at a pressure of 40 mm Hg for 15 seconds while a continuous electrocardiogram(ECG) was recorded. The manoeuvre was repeated three times with one minute interval in between and results were expressed as: Valsalva ratio = longest R-R interval after the manoeuvre ÷ shortest R-R interval during the manoeuvre. The mean of the three Valsalva ratios was taken as the finalvalue.

**Heart rate (R-R interval) variation during deep breathing**

The subject was instructed to breathe deeply at six breaths/min ( five seconds "in" and five seconds "out") for one minute. An ECG was taken through out the period of deep breathing and onset of each inspiration and expiration was inscribed on ECG paper. The maximum and minimum R-R intervals during each breathing cycle were measured with a scale and converted to beats/min. The results of the test were expressed as the mean of the difference between maximum and minimum cardiac rates for the six measured cycles in beats/min.

**Immediate heart rate response to standing**

The test was conducted with the subject lying quietly on a bed while the heart rate was recorded continuously on an electrocardiograph. The patient was then asked to stand unaided and the point atstarting to stand was marked on ECG paper. The shortest R-Rinterval at or around the 15th beat and the longest R-R intervalat around the 30th beat after starting to stand were measured with a ruler. The characteristic heart rate response was expressed by 30:15 ratios. Interpretation of tests was based on the works of Ewing and Clarke. The patients were categorised as normal, if none of the tests was abnormal; with early parasympathetic damage, if results of one of the three tests of parasympatheticwas abnormal; with definite parasympathetic damage, if two or more of the three tests of parasympathetic functionwere abnormal; and with combined damage, if one or both thetests of the sympathetic function were abnormal in additionto parasympathetic damage. For the purpose of the above mentionedclassification the borderlinetests were interpreted as normal.

A scoring system like the one suggested by Bellavere*et al* wasalso utilized to assess the extent of autonomic nervous damage[28]For each test "0" score was given for normal, "1" for borderline,and "2" for an abnormal value. By adding the score of each ofthe five standard tests of autonomic function, total autonomicfunction score was determined for every subject.

A comparisonof frequency of symptoms of autonomic dysfunction was made betweencirrhotics and controls, and between alcoholic and non-alcoholicgroups. A simple set of clinical and laboratory features as devisedby Child and Turcotte (later modified by Pugh and named Child-Pughcriteria) were used in the study to quantify the severity ofliver damage in patients. Scoring is done on the basis of degree of ascites, encephalopathy, hypoalbuminaemia, hyperbilirubinaemia, and hypoprothrombinaemia.

Each of the parameters score in an individual is added to classify a patient as belonging to Child class A, B, or C This grading of cirrhosiswas originally devised to help select patients with cirrhosis for portal systemic shunt surgery and it has been shown to have prognostic value in several studies.

**Picture 1: Blood pressure response to sustained Hand Grip**

**Picture 2: Resting Heart rate variability.**

**Results:**

The study group includes 40 patients with Cirrhosis (20 alcoholics and 20 non-alcoholics) and 40 age and sex matchedcontrols. Male: female ratio was 3:1. Twenty three (57.5%) were below 40 years of age. Common autonomic symptoms observed were dizziness while

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standing( 75%), pain in extremities(7.5%), palpitation(12.5%), and constipation (5%). Nine (22.5%) had family history of jaundice. Of which 3 had HBsAg positive, 2 were diagnosed to have Wilson disease and remaining 4 did not have any identifiable etiologies.

Eleven (27%) patients had recent UGI bleed.Upper GI endoscopy showed Grade I (17), Grade II (15), Grade III (5) and 3 had no esophageal varices.

Eighty percent (32) of patients with Cirrhosis were foundto have evidence of autonomic Dysfunction. Of these, six (15%)patients had early parasympathetic damage, ten (25%) had definiteparasympathetic damage, and sixteen (40%) had combined (that is,both parasympathetic and sympathetic) damage.

Eighteen (90%) ofthe alcoholics and fourteen (70%) of the non-alcoholics had autonomicdysfunction.. Moreover, there was no significant association between subjective symptoms of autonomic dysfunction and objective evidence of autonomic damageas assessed by autonomic function tests. Autonomic dysfunction was significantly more frequent in advanced liver disease compared with early liver damage. One patient (50%)in Child A group, Eighteen (75%) out of 24 patients with Chronic liver disease belonging to Child class B and 13 (92.85%) of the 14 patients belonging to Child class C had autonomic dysfunction..

The mean total autonomic function score were 0.45 for controls ,3.95 in Child class B and 6.53 in class C.(p value = 0.03) by (Mann-Whitney U test).The mean autonomic function scores for alcoholics and and non-alcoholics were 5.70 and 3.65 respectively.( p value = 0.72 by Mann-Whitney U test).In this study, heart rate response to standing was the most frequently (22 out of 40 patients) abnormal test in test group. In the present study, seven patients had abnormal heart rate response to deep breathing, twelve had abnormal blood pressure response to sustainedhandgrip, and eleven patients had an abnormal Valsalva ratio.

**Table.1:** Interpretation of autonomic function tests as normal, borderline, or abnormal depending on the value of the parameter measured

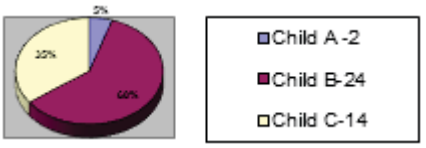
| Test | Predominant Autonomicfunction tested | Normal | Border line | Abnormal |
|---|---|---|---|---|
| Valsalva ratio | parasympathatic | >1.21 | 1.11-1.20 | <1.10 |
| Deep breathing (Max-Min heart beat /min) | parasympathetic | >15 | 11-14 | <10 |
| Heart response to standing (30:15 ratio) | parasympathetic | >1.04 | 1.01-1.03 | <1.00 |
| BP response to standing ( fall in blood pressure in mm Hg) | Sympathetic | <10 | 11-29 | >30 |
| BP response to sustained hand Grip (in crease in diastolic pressure in mm of Hg) | Sympathetic | >16 | 11-15 | <10 |

**Table.2** Distribution of autonomic dysfunction according to Child class

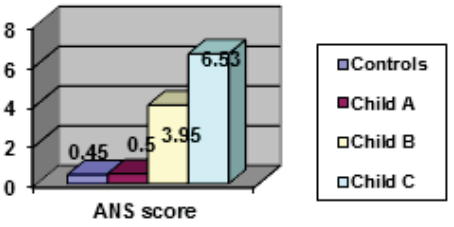
| Group | Child class A (n=2) | Child class B (n=24) | Child class C (n=14) |
|---|---|---|---|
| Early parasympathetic damage | 1 | 4 | 1 |
| Definite parasympathetic damage | 0 | 6 | 4 |
| Combined damage | 0 | 8 | 8 |
| Total | 1 | 18 | 13 |

**Table. 3** Distribution of autonomic dysfunction in alcoholics and non alcoholics

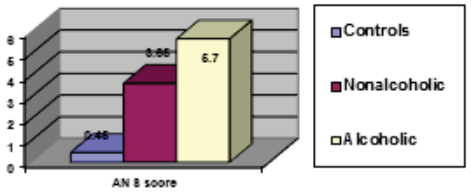
| | Parasympathetic damage | | | |
|---|---|---|---|---|
| Group | early | definite | sympathetic | combined |
| Total (n=40) | 6 | 10 | 16 | 16 |
| Alcoholics (n=20) | 2 | 6 | 10 | 10 |
| Non Alcoholics (n=20) | 4 | 4 | 6 | 6 |




**Graph: 1** Distribution of Child Class in the study population




**Graph: 2.** Disatribution of autonomic score in patients according to Child class




**Graph: 3.** Distribution of autonomic score in alcoholics and non alcoholics

**Discussion:**

Autonomic nervous dysfunction is a known complication of diabetes[7] and alcohol abuse. Autonomic damage is expected in some patients with alcohol related cirrhosis since autonomic dysfunction, especially of vagal origin, is seen in chronic alcoholics[8].Evidence for vagal neuropathy in alcoholic cirrhosis is wellestablished by various studies[9] However, in non-alcoholiccirrhosis there are conflicting reports.[10]

Patients with cirrhosis and ascites have an activation of the sympathetic nervous system, as suggested by a higher than normal level of plasma norepinephrine, an augmented total body and individual organ norepinephrine spill-over rates, and an increased sympathetic nerve activity directly assessed by micro neurographic techniques. The activation of the sympathetic nervous system is believed to playa major role in the pathogenesis of sodium retention and ascites has suggested by the inverse relationship between plasma norepinephrine and the urinary sodium excretion that is often observed in these patients. The possible role of the autonomic nervous system in the regulation of systemic hemodynamics in cirrhosis has been evaluated using cardiovascular tests such as the deep breathing, the 30:15 ratio, and the Valsalva ratio tests, which are considered to estimate parasympathetic activity. The results of these tests were frequently abnormal in patients with both alcoholic and nonalcoholic liver diseases. Indeed, 43%of patients with

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nonalcoholic liver diseases had an abnormal Valsalvaratio, RR variations in deep breathing, and response to intravenous atropine, suggesting a dysfunctionof the parasympathetic nervous system.

In our study, 32 of the 40 chronic liver disease patients (80%) were found to have an abnormal result in one or more autonomic function tests. However, Barter and Tanner in their study of 30 subjects report edevidence of parasympathetic damage in 16% and of combined parasympathetic and sympathetic neuropathy in an additional 20%..The lower frequency of autonomic dysfunction in their study could be due to the fact that they included only 14 subjects with alcoholicliver disease while the rest had an alcohol dependence problemonly.

Szalay*et al* in their evaluation of 121 patients withchronic alcoholism—33 without liver disease, 33 with fattyliver, 33 with cirrhosis, 10 with biliary cirrhosis, and 12with cirrhosis of another origin—found autonomic reflexdamage in all. They observed significantly more damage in those with liver disease. Hendrickse and Triger reported cardiovascularautonomic dysfunction with predominantly parasympathetic abnormalityin 35% of the patients with chronic liver disease.[11]Hendrickse*et al* in another study reported vagal neuropathyin 45% of the 60 patients of chronic liver disease studied.. The lower frequency of neuropathy is probably due to inclusion of mostly Child class A patients in the study (57 of the 60patients)[12]. Moreover, the study included a heterogeneous group of chronic liver disease patients with varying degrees of liver damage. In the present study, only one patient belonged to Childclass A and the rest were class B or C.

Gentile *et al* foundautonomic dysfunction in 60% (71% in the alcoholic group and57% in the non-alcoholic group) of the 113 cirrhotics studied.[13] Like in the present study, alteration of parasympathetic functionwas significantly more frequent than that of sympathetic function.Dillon *et al* also detected abnormal cardiovascular reflexesin 60% of 70 cirrhotics.[14] Their study group included as manyas 42 patients belonging to Child class A and only 15 patientsin class C.

In the present study, eighteen (75%) out of 24 patients belongingto Child class B had autonomic dysfunction while 13 (92.85%) of the 14 patients in class C had impaired autonomic function.One patient (50%) in Child class A had autonomic damage. The mean total autonomic function score were 0.45 for controls were 0.45 for controls , 3.95 inChild class B and 6.53 in class C. .(p value = 0.03) The mean autonomic function scores for alcoholics and and non-alcoholics were 5.70 and 3.65 respectively. These findings are similar to the observations of most other studies,[15,16] which reported increasing frequency of autonomic dysfunction with increasing severity of liver damage.

Hendrickse and Triger reported a strong correlation between the abnormal tests and Child-Pugh score (p<0.0001). In their study, they found autonomic dysfunction in 69% of Childclass B and C patients and 23% in class A patients (p<0.0001).On the contrary, Gonzalez-Reimer *et al* in their study of 33alcoholics, 20 of them cirrhotics, found a weak correlation between liver function and both autonomic and peripheral neuropathy.

Statistical comparison of cirrhotics and controls and alcoholicsand non-alcoholics revealed that light headedness on standingwas significantly more frequent in cirrhotics compared withcontrols (p=0.001). However, no statistically significant associationwas noted between other symptoms or signs of autonomic dysfunction.This is similar to the findings of most of the studies availablewhich found poor correlation between symptoms of autonomic dysfunctionand objective evidence of autonomic dysfunction as assessed bythe autonomic function tests[17,18]. In our study, no statisticallysignificant difference was observed for various clinical featuresand laboratory parameters of liver failure between those withand without autonomic dysfunction. This is in contrast to thefindings of Hendrickse*et al* who observed that patients withvagal neuropathy were significantly older and tended to havelower serum albumin than those with normal cardiovascular test.[19,20]

In our study, heart rate response to standing was the most frequently(22 out of 40 patients) abnormal test in test group. Barterand Tanner in their study noted the heart rate response to standingas the most sensitive test with high specificity. Thuluvath and Triger in their study reported the heart rate response todeep breathing as the most sensitive test. However, it is noteworthythat this test depends on the cooperation of the subject andis, thus not as reproducible as the heart rate response to standing..

Gentile *et al* remarked that deep breathing test and hand griptests are the most influenced by the compliance of the patient. In the study, they found the deep breathing test and lying to standing (heart rate response) tests to be most altered and the most sensitive and specific tests respectively. . In the present study, seven patients had abnormal heart rate response to deep breathing, twelve had abnormal blood pressure response to sustainedhandgrip, and eleven patients had an abnormal Valsalva ratio. Considering the adverse prognostic implications of autonomic dysfunction reported in cirrhotics, further prospective studies involving a larger number of patients are required to find out the factors responsible for the derangement and remedial measures if possible.

**Conclusion:**

This study shows that autonomic dysfunction is common in patients with cirrhosis and it was comparable frequency both in alcoholics and non-alcoholics. It increases in severity with increase in severity of liver damage, suggesting that liver damage contributes to the autonomic neurological dysfunction

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