A study on Autonomic Dysfunction in Patients with Cirrhosis of Liver

Background:
Cirrhosis of the liver leads to a number of complications, some of which may eventually prove fatal. It has been observed that alcohols with liver damage have higher frequency of neuropathy than those without it. There are reports of association of chronic liver disease with autonomic neuropathy. However, conflicting reports have also appeared causing much confusion. Patients with cirrhosis and portal hypertension develop a hyperdynamic circulation, with increased blood volume and cardiac output, and a reduced peripheral vascular resistance. This disorder has been related to portal hypertension-induced arterial vasodilatation in the peripheral and splanchnic beds, but other factors may contribute, such as abnormally high levels of circulating vasodilators and false neurotransmitters.

Autonomic dysfunction (AD) is seen in both alcohol-related and non-alcohol-related liver disease, and when present is an independent predictor of mortality. 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.

Orthostatic hypotension is one of the first recognized symptoms and typically is the most disabling. Palpitations, nausea, tremulousness, presyncope with light-headedness, visual blurring, tinnitus, and even chest pain and shortness 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. 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, hypoalimentation, and altered sense of taste).

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 2006 to March 2007, 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 years 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, ultrasound 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 assessment was 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, Aspartic acid protein, albumin, SAAG, amylase, cell count and cytology, viral markers like HBsAg, AntiHCVab, serum Ceruloplasmin 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 subjected to a battery of five standard autonomic function tests as detailed below.

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 ascites, fever, anorexia, altered sleep pattern, bleeding tendency, spider nevi, palmar erythema, duodenal ulcer, gynaecomastia and asthenia. High SAAG ascites and or evidence of portal hypertension by clinical, endoscopic, Doppler ultrasound examination, and liver biopsies were performed whenever feasible.

**EXCLUSION CRITERIA**

Patients diagnosed as acute viral hepatitis, Liver secondaries with 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 NCPE could not ruled out with certain after exhaustive testing. Subjects who were known diabetes mellitus, ischemic heart disease and other medical conditions, and drugs that causes autonomic disturbances were excluded from the study.

**Tests reflecting sympathetic damage**

Blood pressure response to standing

This test measured the subject’s blood pressure with an sphygmomanometer while he was lying quietly and one minute after which he was made to stand up. The postural fall in blood pressure was taken as the difference between the systolic pressure lying and the systolic blood pressure standing. The test was repeated three times and the mean was calculated.

Blood pressure response to sustained hand grip

The blood pressure of the patient was taken three times before the maneuver. A modified sphygmomanometer was used for the sustained hand grip maneuver. The patient was asked to grip the inflatable rubber bag and apply maximum voluntary pressure possible. Reading from the attached mercury manometer was taken at maximum voluntary contraction.

Thereafter, the patient was asked to maintain 30% of maximum voluntary contraction for as long as possible up to five minutes. Blood pressure was measured each minute intervals during the hand grip. The result was expressed as the difference between the highest diastolic blood pressure during the hand grip exercise and the mean of the three diastolic blood pressure readings before the hand grip began.

**Tests reflecting cardiac parasympathetic damage**

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

**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 throughout 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 at starting to stand was marked on ECG paper. The shortest R-R interval at or around the 15th beat and the longest R-R interval at or 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 categorized as normal, if none of the tests was abnormal; with early parasympathetic damage, if results of one of the three tests of parasympathetic ratios was abnormal; with 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. For the purpose of the above mentioned classification the borderlinetests were interpreted as normal.

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

A comparison of frequency of symptoms of autonomic dysfunction was made between cirrhotics and controls, and between alcoholic and non-alcoholic groups. A simple set of clinical and laboratory features as devised by Child and Turcotte (later modified by Pugh and named Child-Pugh criteria) were used in the study to quantify the severity of liver 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 cirrhosis was 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.
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 found to have evidence of autonomic Dysfunction. Of these, six (15%) patients had early parasympathetic damage, ten (25%) had definite parasympathetic damage, and sixteen (40%) had combined (that is, both parasympathetic and sympathetic) damage.

Eighteen (90%) of the alcoholics and fourteen (70%) of the non-alcoholics had autonomic dysfunction. Moreover, there was no significant association between subjective symptoms of autonomic dysfunction and objective evidence of autonomic damage 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 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 sustained handgrip, 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

<table>
<thead>
<tr>
<th>Test</th>
<th>Predominant Autonomic function tested</th>
<th>Normal</th>
<th>Border line</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valsalva ratio</td>
<td>parasympathetic</td>
<td>&gt;1.21</td>
<td>1.11-1.20</td>
<td>&lt;1.10</td>
</tr>
<tr>
<td>Deep breathing</td>
<td>parasympathetic</td>
<td>&gt;15</td>
<td>11-14</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Heart response to standing (30:15 ratio)</td>
<td>parasympathetic</td>
<td>&gt;1.04</td>
<td>1.01-1.03</td>
<td>&lt;1.00</td>
</tr>
<tr>
<td>BP response to standing (fall in blood pressure in mm Hg)</td>
<td>Sympathetic</td>
<td>&lt;10</td>
<td>11-29</td>
<td>&gt;30</td>
</tr>
<tr>
<td>BP response to sustained hand Grip (in increase in diastolic pressure in mm of Hg)</td>
<td>Sympathetic</td>
<td>&gt;16</td>
<td>11-15</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

Table 2: Distribution of autonomic dysfunction according to Child class

<table>
<thead>
<tr>
<th>Group</th>
<th>Child class A (n=2)</th>
<th>Child class B (n=24)</th>
<th>Child class C (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early parasympathetic damage</td>
<td>1</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Definite parasympathetic damage</td>
<td>0</td>
<td>6</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 3: Distribution of autonomic dysfunction in alcoholics and non alcoholics

<table>
<thead>
<tr>
<th>Group</th>
<th>Parasympathetic damage</th>
<th>Sympathetic damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n=40)</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Alcoholics (n=20)</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Non Alcoholics (n=20)</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Graph 1: Distribution of Child Class in the study population

Graph 2: Distribution 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 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. Evidence for vagal neuropathy in alcoholic cirrhosis is well established by various studies. However, in non-alcoholic cirrhosis there are conflicting reports.

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 play a 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 non-alcoholic liver diseases. Indeed, 43% of patients with...
nonalcoholic liver diseases had an abnormal Valsalvatario, BR variations in deep breathing, and response to intravenous atropine, suggesting a dysfunction of 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 evidence 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 alcoholic liver disease while the rest had an alcohol dependence problemonly.

Szalayet et al in their evaluation of 121 patients with chronic alcoholism—33 without liver disease, 33 with fatty liver, 33 with cirrhosis, 10 with biliary cirrhosis, and 12 with cirrhosis of another origin—found autonomic reflex damage in all. They observed significantly more damage in those with liver disease. Hendrickse and Triger reported cardiovascularautonomic dysfunction with predominantly parasympathetic abnormality in 35% of the patients with chronic liver disease. Hendrickse et al in another study reported vagal neuropathy in 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 60 patients). 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 Child class A and the rest were class B or C.

Gentile et al found autonomic dysfunction in 60% (71% in the alcoholic group and 57% in the non-alcoholic group) of the 113 cirrhotics studied. Like in the present study, alteration of parasympathetic function was significantly more frequent than that of sympathetic function. Dillon et al also detected abnormal cardiovascular reflexes in 60% of 70 cirrhotics. Their study group included as many as 42 patients belonging to Child class A and only 15 patients in class C.

In the present study, eighteen (75%) out of 24 patients belonging to 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 was 0.45 for controls, 3.95 in Child class B and 6.53 in class C. (p value = 0.03) The mean autonomic function scores for alcohols and non-alcohols were 5.70 and 3.65 respectively. These findings are similar to the observations of most other studies, suggesting a dysfunction of the parasympathetic nervous system.

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

Gentile et al remarked that deep breathing test and hand grip tests 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 sustained handgrip, and eleven patients had an abnormal Valsalva ratio. Considering the adverse prognostic implications of autonomic dysfunction reported in cirrhosis, 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.

References: