International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2013): 6.14 | Impact Factor (2015): 6.391

Evaluation of Autonomic Neuropathy in Chronic Alcoholic Liver Disease

Dr. Robinson Ningshen[1], Dr. Sanjiv Kr Sharma[2], Dr. Rajeev S.A[3], Dr. Th Suraj Singh[4], Dr. N Biplab Singh[5]

Abstract: ***Background**: Autonomic neuropathy (AN) is quiet common in chronic alcoholic liver disease. Long term alcohol consumption may produce wide ranging effect on almost all body tissues, including the autonomic and peripheral nervous systems. Clinical symptoms of autonomic failure generally appear when the polyneuropathy is severe. **Objective**: To study the prevalence of autonomic dysfunction in patients with chronic alcoholic liver disease and its correlation with Child Turcotte- Pugh score. **Materials and Methods**: A cross sectional study was done on 80 patients of chronic alcoholic liver disease. Apart from clinical examination and routine investigation, polyrite was used to carry out autonomic function test. **Results**: Out of 80 patients autonomic dysfunction was observed in 58 (72.5%) patients. Early autonomic involvement was found in 30 (37.5%), definite involvement in 10 (12.5%), severe involvement in 18 (22.5%) patients. **Conclusion**: Autonomic neuropathy is common in chronic alcoholic liver disease and its severity increases with increase in Child Turcotte- Pugh score.*

Keywords: Autonomic neuropathy, chronic alcoholic liver disease, alcoholic liver cirrhosis

1. Introduction

Long term alcohol consumption produces wide ranging effects on almost all body tissues, including the autonomic and peripheral nervous systems[(1)]. Autonomic involvement may contribute to high mortality rate among alcoholics[(2)]. Autonomic dysfunction may present clinically as pupillary abnormalities, sweating disturbances, loss of lacrimation and salivation, cardiovascular disturbances (postural hypotension, persistent tachycardia or bradycardia), gastrointestinal disturbances, genitourinary disturbances and metabolic disturbances like recurrent hypoglycaemia attacks due to hypoglycaemic unawareness[(1)]. Autonomic dysfunction has been noted in cirrhosis in the form of hyperdynamic circulation, resting tachycardia, relative hypotension and diminished vascular resistance and is a poor prognostic indicator in patients with advanced liver disease[(3)]. Autonomic neuropathy (AN) is recognized in 68%-80% of patients with cirrhosis[(4-6)]. Cardiovascular autonomic neuropathy represents a serious complication as it carries a 5-fold risk of mortality in patients with chronic liver diseases[(7)]. In a 10-months long follow-up study in patients awaiting liver transplantation the mortality was significantly higher in patients with AN (27%) compared to those without AN (0%), suggesting that AN should be taken into consideration for early liver transplantation[(8)]. Parasympathetic dysfunction was more common than sympathetic dysfunction (60% versus 21%) and the overall prevalence of autonomic dysfunction decreased 6 months after transplant[(4)]. The QT interval on electrocardiography, a surrogate marker of autonomic dysfunction, is prolonged in patients with cirrhosis. This abnormality resolves in the majority of patients after liver transplantation, although a small percentage of patients remain abnormal after transplant[(9,10,11,12)]. Therefore early diagnosis of AN is required in patients of liver disease to reduce mortality by liver transplantation. Alcohol abuse is very common in northeast part of india and widely prevalent among the general population of Manipur, a state in northeast India. In Manipur, 47% of male and 2% of female drink alcohol[(13)]. But the morbidity and mortality data of autonomic neuropathy in relation with alcoholic liver disease is lacking from this part of india. The present study was undertaken to see the prevalence of autonomic neuropathy in patients with chronic alcoholic liver disease and to determine the degree of severity of alcoholic liver disease and its correlation with autonomic profile.

2. Materials and Methods

A cross sectional study was carried out from Oct 2011- Sept 2013 by using Battery of 5 autonomic function tests [(13)]. The tests were performed in patients suffering from chronic alcoholic liver disease after getting approval from the Institutional Ethical Committee, RIMS. A total of 80 patients who had significant history of alcoholism (men 40-80 gm/day and women 20-40 gm/day for 10-12 years) were enrolled for the study. Exclusion criteria includes Hepatitis B, Hepatitis C, HIV infected patients, Autoimmune hepatitis, Drugs causing autonomic dysfunction, Other causes of dysautonomia (multisystem atrophy, parkinsonism, diabetes mellitus, hypertension, renal failure, advanced age). Written informed consent was obtained from all the subjects. Prior to testing of autonomic nervous function, all subjects underwent a detailed history taking including symptoms of autonomic nervous system and examination using a proforma, relevant investigation including complete blood count, liver function test, kidney function test, prothrombin time and international normalized ratio, random blood sugar, Anti-nuclear antibody, HBsAg, Hep-C virus- Ab, HIV-1 and 2, ascitic fluid analysis, ultrasonography (W/A), upper G.I endoscopy. Then autonomic functions were carried out by using the polyrite model no. 206, Recorders and Medicare Systems (RMS), Chandigarh.

On the day of the test no cigarette, nicotine, coffee, food or drugs per orally or other route were permitted 3 hrs prior to the test. On reaching the department, they were made to rest for at least 15 minutes in the laboratory room which had a quiet ambient temperature of 19-25 degree Celsius. Patients were made to wear loose gowns and not allowed to wear metallic objects. Assessment of autonomic function was done by using different parameters like baseline cardio-respiratory, parasympathetic and sympathetic. Baseline cardio-respiratory status was recorded in the form of heart

rate, respiratory rate, systolic and diastolic blood pressure. Polyrite has inbuilt ECG channel for recording electrocardiogram. Lead II of the ECG was selected for heart rate and recorded in supine position for a period of 1 minute.

Parasympathetic parameters were assessed by following test. Heart rate variation to deep and slow breathing (HRDB) was done. After 5 minutes rest in supine position, the subjects were instructed to take deep and slow breath at the rate of 6 breaths/min (3 sec inspiration, 2 sec pause, 3 sec expiration and 2 sec pause) for a period of 2 minutes. 6 cycles were repeated in each test. The mean of the minimum R-R interval in the six inspiratory cycles was calculated and heart rate determined. The mean of the maximum R-R interval in the six expiratory cycles of the same tracing were calculated with the use of Polyrite and timer. [Expiration: Inspiration = Maximum R-R interval during Expiration/ Minimum R-R interval during inspiration]. Heart rate response of Valsalva manoeuvre was assessed by using Polyrite, timer and modified mercurial sphygmomanometer. The heart rate was recorded continuously on polyrite before, during and 30 seconds after the manoeuvre. [Valsalva ratio= Longest R-R interval after manoeuvre (phase IV)/ Shortest R-R interval during the manoeuvre (phase II)][14]. Heart rate response to standing (30:15) was assessed after a complete rest of 15 minutes in supine position, ECG recording was started and the subject assumes erect posture from the supine position within 3 seconds with continuous ECG recording for 30 seconds or more in erect posture. The ratio of the longest R-R around 30th beat after standing to the shortest R-R interval around 15th beat after standing were calculated for the result of 30:15 ratio.

Sympathetic parameters were assessed by following tests. Blood pressure response to postural change was measured by using Mercurial sphygmomanometer (Novaphone 600). After 5 minutes of rest in supine position, basal blood pressure was recorded. Then the subject was asked to stand up immediately and remain still without movement. After 30 seconds, 1 minute and 3 minute respectively, blood pressure was recorded. The difference of the systolic blood pressure between the one recorded while lying supine and in erect posture after 0.5 minutes of standing was calculated. The fall in systolic blood pressure was used as the result of change in posture test. Blood pressure response to sustained isometric handgrip (IHG) was also measured in which a basal blood pressure was measured in a sitting position first, then the subject was asked to perform maximum grip of the handgrip dynamometer and the maximum capacity from the graduation marking was noted down. After 5 minutes in sitting position, the subject was asked to hold his grip with 30% of the maximum capacity for 4 minutes. During the sustained grip, blood pressure was measured every 2 minutes. The rise in diastolic blood pressure just before the release of the grip, in comparison to the basal was calculated and taken as the result of IHG. Normal-16mmHg, Borderline-11-15 mmHg, Abnormal-10 mmHg[15].

3. Results and Observation

Mean age of the study population was 46±9.70 years. Study population include 79(98.8%) male and 1(1.2%) female. Normal BMI (18.5-22.9)[16] observed in 40(50%), <18.5 in 13(16.3%), overweight (23-24.9) in 13(16.3%), obese I(25-29.9) in 14(17.5%) and obese II(>30) in none. 23 patients (28.8%) were smoker, mean alcohol intake was 762.5± 458.90 ml/day, mean duration was 12.06±7.46 years. None of the participants had diabetes mellitus, hypertension, chronic kidney disease or HIV infection. Autonomic function tests were carried out on 80 patients and autonomic dysfunction was observed in 58(72.5%) patients. Early autonomic involvement was found in 30(37.5%), definite involvement in 10(12.5%), severe involvement in 18(22.5%) while normal autonomic function was documented in the rest 22(27.5%). Parasympathetic involvement was noticed in 58(100%) patients while 18(33%) had both parasympathetic and sympathetic involvement. Heart rate response to standing (30:15 ratio) was the most altered parasympathetic test in 39(67.2%) followed by heart rate response of valsalva manoeuvre (VR) in 32(55.2%) and heart rate variation to deep and slow breathing (E:I) in 29(50%).

Autonomic symptoms was assessed by questionnaire and it was found that most common was weakness in 63(78.8%) followed by dizziness in 56(70%), vasomotor symptoms like sweating in 52(65%) and palpitation in 45(56.3%). Baseline cardio-respiratory parameters of study group was mean resting heart rate 87.62±15.15 beats/minute, mean resting systolic B.P 116.72±17.38 mmHg, mean resting diastolic B.P 78.6±10.28 mmHg, mean resting respiratory rate 19.42±4.42 per minute.

AN was found in 44(77.2%) patients more than 40 years of age and 14(60.9%) patients less than 40 years of age. Though AN was more common among those more than 40 years of age, the difference was not statistically significant (P= 0.139). On routine laboratory test, anemia was observed in 55(68.8%), leukocytosis in 14(17.5%), thrombocytopenia in 23(28.8%). Patients belonging to child class A were 26(32.5%), class B in 19(23.8%) and class C in 35(43.7%). Elevated SGOT was found (>5 times) in 10 patient and 9 had autonomic neuropathy. SGPT (> 5 times) was found 3(3.8%) and all had autonomic neuropathy. Spontaneous bacterial peritonitis was observed in 7(8.8%) and all had neuropathy. Ultrasonography (W/A) was suggestive of fatty liver in 42(52.5%), cirrhosis in 38(47.5%) and portal hypertension in 49(61.3%) patients. 44 out of 49 patients of portal hypertension had autonomic neuropathy. Grade I or II varices were found in 29(36.25%) and grade III or IV varices in 12(15%). Among 41 patients with varices, 36(87.8%) had autonomic neuropathy.

A Battery of 5 autonomic function test were performed for assessment of autonomic functions in the study population- 3 parasympathetic and 2 sympathetic. Among parasympathetic tests, mean E:I (heart rate response to deep breathing) was 1.10±0.07, mean VR (heart rate response to Valsalva manoeuvre was 1.27±0.23 and mean 30:15 (heart rate response to standing) was1.10±0.10. Out of 2 sympathetic tests performed, mean Δ DBP obtained after sustained handgrip for 4 minute was 14.67±10.48 mmHg and mean Δ SBP (fall in blood pressure at 0.5 minutes of standing) was 8.78±8.33 mmHg. AN was graded into normal, early, definite, severe or atypical. Normal autonomic function was observed in 22(27.5%), early in 30(37.5%), definite in 10(12.5%) and severe in 18(22.5%).

Child Turcotte Pugh (CTP scoring) was used for correlation of autonomic neuropathy with the severity of chronic liver disease. Among 26 patients with child class A, normal autonomic function was observed in 16(61.5%), early and definite neuropathy in 10(38.5%) and severe neuropathy in 0(0%). 19 patients with Child class B, normal autonomic function was found in 2(10.5%), early and definite neuropathy in 10(52.6%) and severe neuropathy in 7(36.9%). 35 patients with Child class C, normal autonomic function was seen in 4(11.4%), early and definite neuropathy in 20(57.2%) and severe neuropathy in 11(31.4%). AN was documented in 10(38.5%) patients with class A, 17(89.5%) with class B and 31(88.6%) with class C. The correlation between Child-Pugh scoring and severity of autonomic dysfunction was found to be significant with a P value of 0.000. Among patients with decompensated (CTP ≥7) liver disease, normal autonomic function was observed in 6(11.1%), early and definite neuropathy in 30(55.6%) and severe neuropathy in 18(33.3%). Among compensated (CTP <7) liver disease, normal autonomic function was found in 16(61.5%), early and definite neuropathy in 10(38.5%) and none had severe autonomic neuropathy. Autonomic neuropathy was more common among decompensated alcoholic liver disease (88.9%) compared to compensated liver disease(38.5%). Severe autonomic neuropathy was only seen in decompensated liver disease (P value= 0.000, statistically significant).

Correlation of autonomic neuropathy with liver disease:

Liver disease	Presence of autonomic neuropathy			Total n (%)	Chi square Value	d.f	P value
	Normal	Early and definite	Severe				
Compensated	16 (61.5%)	10 (38.5%)	0	26 (100)			0.000
Decompensated	6 (11.1%)	30 (55.6%)	18 (33.3%)	54 (100)			
Total	22	40	18	80	25.921	1	

P value<0.05 was considered to be significant.

Among 14 patients with abnormal total leukocyte count (TLC >10,000), incidence of AN was higher. But difference was not statistically significant (P-value= 0.328). 23 (100%) patients with thrombocytopenia (<1.5 lakhs) had AN, when compared to 35 (61.4%) among 57 patients with normal platelet count (P-value= 0.000). Among 10 patients with high SGOT (>5 times), 9(90%) had AN, as compared to 49(70%) patients among 70 patients with <5 times elevation (P-value= 0.270). Of the 58 patients with AN, 3(100%) had SGPT > 5 times UNL and 55 had SGPT <5 times UNL (P-value= 0.557). Out of the 38 cirrhotic patients 34(89.5%) had autonomic dysfunction and 24(57.1%) patients out of 42 non-cirrhotics had autonomic dysfunction (P-value= 0.001, statistically significant). There were 7 patients with spontaneous bacterial peritonitis and all had AN (P-value= 0.181). Among 41 patients with varices, 36(87.8%) had AN as compared with 22(56.4%) among 39 patients who did not have varices (P-value= 0.02, statistically significant).

4. Discussion

Alcohol is one of the most common etiologies of liver disease apart from hepatitis B and C, non-alcoholic fatty liver disease, autoimmune hepatitis and others. Liver disease due to chronic alcoholic consumption is associated with AN, which is considered a poor prognostic factor according to Fleckenstein[17] et al. In this cross sectional study conducted in 80 chronic alcoholic liver disease patients, maximum cases were in the age group of 41-50 years with 25 cases (38.75%) followed by 51-60 years with 22 cases (27.5%). Mean age of the study population was 46.16±9.70 years. This data is comparable with previous studies by Joye Varghese[18] et al. In this study, older patients (>40 years) appeared to have more AN 44(77.2%) compared to age <40 years.

In our study, autonomic dysfunction was documented in 72.5% of patients. The data is similar to Bajaj[4] et al who studied autonomic dysfunction in hepatic cirrhosis (80%). In our study 58 patients out of 80 had AN, out of which all had parasympathetic dysfunction while 18(33%) had both parasympathetic and sympathetic dysfunction. Hendrickse[19] et al, reported vagal neuropathy in 45% of the 60 patients with chronic liver disease. Gentile[20] et al found AN in 60% (71% in the alcoholic group and 57% in the non-alcoholic group) of the 113 cirrhotics studied. Dillon[21] et al detected abnormal cardiovascular reflexes in 60% of 70 cirrhosis. Their study group included 42 patients with Child class A and 15 patients in class C. Majority of our patients did not show orthostatic decrease in blood pressure suggesting relatively intact sympathetic function. This is consistent with other previous studies[2,17,22,23].

In our study, impaired autonomic function was seen in 38.5%, 89.5%, 88.6% of patients in Child Pugh class A, B, C respectively. Severe AN was documented in 0(0%) in class A, 7 (36.9%) in class B and 11(31.4) in class C. There was a positive correlation between increasing Child class and the severity of AN (P-value< 0.001). Hendrickse and Triger[24] reported a strong correlation between the abnormal tests and Child-Pugh score. In their study, they found AN in 69% of Child class B and C patients and 23% in class A patients (P-value < 0.0001).

In our study, the variables related to liver disease severity that correlated with AN significantly were low platelet count (P-value= 0.000), Child-Turcotte Pugh score (P-value= 0.000), presence of cirrhosis and portal hypertension on ultrasound and presence of varices (P-value= 0.02). Total leukocyte count (P-value= 0.328), rise in liver enzymes SGOT (P-value= 0.270) and SGPT (P-value= 0.557), spontaneous bacterial peritonitis (P-value= 0.1810) and autonomic symptoms (P-value= 0.220) correlated poorly with the AN. In cirrhotics, the liver enzymes can be normal, making it a poor predictor of AN as evidenced by our study. There were 7 patients with spontaneous bacterial peritonitis and all had AN. Heart rate response to standing (30:15) was the most altered test in 39(67.2%) followed by heart rate response to valsalva maneuver in 32 (55.2%) and heart rate response to deep breathing (E:I) in 29(50%). Bajaj[4] et al

also reported that the most frequent abnormal test was heart rate response to standing (11 out of 20 patients). Similar reports were published by Barter and Tanner[25] and Gentile[20] et al, while Thuluvath and Triger[2] in their study reported the heart rate response to deep breathing as the most sensitive test. J Perez-Pena[27] et al, reported that the overall prevalence of AN among 27 patients decreased 6 months after liver transplantation compared to pre-transplantation (74.1% vs. 48%) due to a significant reduction in definite AN (51.9 vs. 14.8%; $p<0.05$). AN score improved in 70% of cases.

Abnormal heart rate variations in response to rapid deep respiration (E:I) was observed in 11.5% of patients of class A, 63.2% of class B and 40% of class C. Abnormality in heart rate variations in response to Valsalva manoeuvre was found in 3.8% of patients of class A, 47.4% of class B and 62.9% of class C. Abnormal heart rate response to standing (30:15), was found in 26.9% of patients of class A, 36.8% of class B and 71.4% of class C. Abnormal blood pressure response to standing was present in 23.1% of patients of class A, 21.1% of class B and 22.8% of class C. Abnormal blood pressure response to sustained handgrip was present in 7.7% of patients of class A, 42.1% of class B and 54.3% of class C. From our study, it is clear that autonomic dysfunction was common in patients with alcoholic liver disease and majority of abnormalities were in patients of class C, followed by those of class B and lastly those of class A and the difference were statistically significant. Similar results was reported by Fawi et al[26]. This cross-sectional study reveals that out of the 80 patients, autonomic dysfunction was more common in adults (41-50 year age). Early AN was observed in 30(37.5%), definite involvement in 10(12.5%), severe involvement in 18(22.5%) while normal autonomic function was documented in the rest 22(27.5%). Parasympathetic involvement was found in 58(100%) patients with AN and 18(33.3%) had both parasympathetic and sympathetic dysfunction. This study emphasizes the fact that identification of this subset of patients with autonomic dysfunction in alcoholic liver disease can possibly improve survival. Hence autonomic function testing should be a part of routine workup for liver disease in the future and preference should be given for early intervention in such a high risk population. This study is the single largest study in india so far.

References

[1] Monforte R, Estruch R, Valls- Sole J, Nicolas J, Villaita J, Urbano-Marquez A. Autonomic and Peripheral Neuropathy in patients with Chronic Alcoholism: A Dose- Related Toxic Effect of Alcohol. Arch Neurol. 1995;52(1): 45-51.
[2] Thuluvathj PJ, Triger DR, Autonomic neuropathy in chronic liver disease. J Med. 1989; 72: 737-47.
[3] Engstrom JW, Martin JB. Diseases of the autonomic nervous system In: Braunwald E, Hauser SL, Fauci AS, et al,eds. Harrison's Principles of Internal Medicine. Vol 2. 15th ed. New York: McGraw-Hill, 2001: P.2416-21.
[4] Bajaj BK, Agarwal MP, Krishna Ram B. Autonomic neuropathy in patients with hepatic cirrhosis. Postgrad Med 2003;79:408-411.
[5] Trevisani F, Sica G, Mainqua P, Santese G, De Notariis S, Caraceni P, et al. Autonomic dysfunction and hyperdynamic circulation in cirrhosis with ascites. Hepatology1999;30:1387-1392.
[6] Hendrickse MT, Thuluvath PJ, Triger DR. The natural history of autonomic neuropathy in chronic liver disease. *Lancet* 1992; 339: 1462-1464.
[7] Fleckenstein JF, Frank S, Thuluvath PJ. Presence of autonomic neuropathy is a poor prognostic indicator in patients with advanced liver disease. *Hepatology* 1996; 23: 471-475.
[8] Carey EJ, Douglas DD. Effects of orthotopic liver transplantation on the corrected QT interval in patients with end-stage liver disease. Dig Dis Sci 2005;50:320-323.
[9] Mohamed R, Forsey PR, Davies MK, Neuberger JM. Effect of liver transplantation on QT interval prolongation and autonomic dysfunction in end-stage liver disease. Hepatology 1996;23:1128-1134.
[10] Bal JS, Thuluvath PJ. Prolongation of the QTc interval: relationship with etiology and severity of liver disease, mortality, and liver transplantation. Liver Int 2003,23: 243-248.
[11] Garcia Gonzalez M, Hernandez-Madrid A, Lopez-Sanroman A, Candela A, Nuno J, Barcena R. Reversal of QT interval electrocardiographic alterations in patients with cirrhosis undergoing liver transplantation. Transplant Proc 1999;31:2366-2367.
[12] International Institute for population science (IIPS) and Macro International. 2008. National Family Health Survey (NFHS-3), India, 2005-2006: Manipur. Mumbai: IIPS. Available from URL: http://www.nfhsindia.org/ Manipur_report.shtml. (accessed on 21/8/2011).
[13] Punyabati O, Deepak KK, Sharma MP. Autonomic Nervous System reactivity in Irritable Bowel Syndrome. Indian J Gastroenterol. 2000; 19: 122-5.
[14] Wieling W, Karemaker JM, Measurement of heart rate and blood pressure to evaluate disturbances in neurocardiovascular control. In: Mathias CJ, Bannister R. Editors. Autonomic failure. 4th ed. Oxford: Oxford university press: 1999. P. 196-210.
[15] Ewing DJ, Clark BF. Diagnosis and management of diabetic autonomic neuropathy. Br Med J. 1982; 285:916-8.
[16] Kanazawa M, Yshiike N, Osaka T, Numba Y, Zimmet P, Inoue S. Criteria and classification of obesity in Japan and Asia-Oceania. Asia Pacific J Clin Nutr. 2002; 11: 732-7
[17] Fleckenstein JF, Frank SM and Thuluvath PJ. Presence of Autonomic Neuropathy is a poor prognostic indicator in patients with Advanced Liver disease. Hepatology. 1996; 23(3): 471-5
[18] Varghese SJ, Balan N, Naveen B, Selvi KC, Jayapalan K, Jayanthi V. Does autonomic dusfunction in cirrhosis liver influence variceal bleed?. Annals of Hepatology.2007;6(2):104-07.
[19] Hendrickse MT, Thuluvath PJ, Triger DR. Natural History of Autonomic Neuropathy in Chronic Liver Disease. Lancet. 1992; 33(07):1462-4.
[20] Gentile S, Marmo R, Peduto A, Montella F, Coitorti M. Autonomic Neuropathy in Liver Cirrhosis: relationship

with alcoholic etiology and severity of the disease. Ital J Gastroenterol. 1994; 26(2): 53-8.
[21] Dillon JF, Plevris JN, Nolan J, Ewing DJ, Neilson JM, Bouchier IA, et al. Autonomic function in cirrhosis assessed by cardiovascular reflex tests and 24 hour heart rate variability. Am J Gastroenterol. 1994; 89(9): 1544-7.
[22] Kempler P, Varadi A, Szalay F, Oraveez L, Kadar E, Kiss E. Autonomic neuropathy in chronic liver diseases. Gastroenterol J. 1990; 50(4): 187- 9.
[23] Chaudhry V, Corse AM, O'Brian R. Autonomic and peripheral (sensorimotor) neuropathy in chronic liver disease: a clinical and electrophysiologic study. Hepatology. 1999; 29: 1698- 703.
[24] Hendrickse MT, Triger DR. Autonomic dysfunction and hepatic function in chronic liver disease. Gut. 1990; 31: 1164.
[25] Barter F, Tanner AR. Autonomic neuropathy in an alcoholic population. Postgrad. MJ. 1987; 63: 1033- 6.
[26] Dumcke CW, Moller S. Autonomic dysfunction in cirrhosis and portal hypertension. Scand J Clin Lab Invest. 2008; 68(6): 437- 47.
[27] J Perez- Pena, D Rincon, R Banares. Autonomic in end stage cirrhotic patients and evolution after liver transplantation. Transplantation proceedings. 2003;35(5): 1834- 5.