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The increased incidence of vagal neuropathy in cirrhosis

Karaciğer sirozunda vagal nöropati sıklığında artış

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Background/Aims: *Vagal neuropathy, as indicated by alterations in standard cardiovascular tests, is frequently encountered in cirrhosis. Recently, there have been many reports about the increase in frequency of vagal neuropathy, which is a negative prognostic factor increasing mortality in hepatic cirrhosis. This study evaluated the frequency of vagal neuropathy and its relationship to age, sex, etiology, serum albumin and bilirubin levels and also prothrombin time in cirrhosis.* ***Methods:*** *Thirty-five patients with a definite diagnosis of hepatic cirrhosis and a control group comprising 20 healthy volunteers were included in the study. Cardiovascular reflex tests found by Ewing, Clarke, et al. were used to determine the existence of vagal neuropathy.* ***Results:*** *Vagal neuropathy was found to be positive in 20 (57%) patients while it was not detected in any subject in the control group. The incidence of vagal neuropathy was significantly increased in cirrhotic patients compared to the control group ($p<0.001$). The most abnormal test results were the heart rate responses to Valsalva maneuver and to deep breathing. Vagal neuropathy was found to have no significant relationship with etiology, sex, age and serum albumin levels but was more frequent when increased prothrombin time and high serum bilirubin levels existed ($p<0.01$).* ***Conclusion:*** *The incidence of vagal neuropathy is significantly increased in cirrhotic patients.*

Keywords: Cirrhosis, vagal neuropathy, cardiovascular reflex tests.

Amaç: *Standart kardiyovasküler testlerdeki değişikliklerle gösterilen vagal nöropati, sirozda sık görülür. Vagal nöropatinin, karaciğer sirozunda mortaliteyi arttıran kötü bir prognostik faktör olduğunu bildiren yayınların artması üzerine, sirozda vagal nöropati sıklığını ve bunun yaş, cinsiyet, etyoloji, serum albumin ve bilirubin düzeyi ve protrombin zamanı ile ilişkisini araştırdık.* ***Yöntem:*** *Çalışmamıza kesin karaciğer sirozu tanısı almış 35 hasta ve 20 sağlıklı gönüllüden oluşan kontrol grubu alındı. Vagal nöropatinin tespiti için Ewing ve Clarke'ın bulduğu kardiyovasküler refleks testleri kullanıldı.* ***Bulgular:*** *Vagal nöropatinin 20 (% 57) hastada pozitif olduğu tespit edildi ve kontrol grubunda vagal nöropatiye rastlanmadı. Sirozlu hastalarda vagal nöropati sıklığı, kontrol grubuna göre çok ileri düzeyde anlamlı olarak yüksek bulunmuştur ($p<0.001$). En anormal test sonuçları, Valsalva manevrasına ve derin solunuma kalp hızı yanıtlarıydı. Vagal nöropatinin; etyoloji, cinsiyet, yaş ve serum albumin düzeyleriyle anlamlı bir ilişkisinin bulunmadığı; fakat sıklığının, artan protrombin zamanı ve yüksek serum bilirubin düzeylerinin varlığında arttığı tespit edildi ($p<0.01$).* ***Sonuç:*** *Karaciğer sirozlu hastalarda vagal nöropati sıklığı belirgin şekilde artmıştır.*

Anahtar kelimeler: Siroz, vagal nöropati, kardiyovasküler refleks testleri.

INTRODUCTION

Hepatic cirrhosis is extensive fibrosis of the hepatic parenchyma in association with formation of regenerative nodules following irreversible chronic injury of liver (1). The autonomic nervous system innervates vascular and visceral smooth muscles, exocrine and endocrine glands, and parenchymal cells of the various organ systems. Many of the functions governed by the autonomic nervous system include the distribution of blood flow and the maintenance of tissue perfusion, the regulation of blood pressure, the regulation of the volume and composition of the extracellular fluid, the expenditure of metabolic energy. Supply of substrate and the control of visceral smooth muscles and glands (2-5).

It has been reported that vagal neuropathy (VN) is frequently observed and is an important prognostic factor which increases mortality in hepatic cirrhosis. These studies found that the excretion of sodium and water was decreased and levels of ADH, renin, angiotensin II (AII) and norepinefrin were increased in the cirrhotic patients with VN compared with the other cirrhotic patients. The reason for the increased mortality in hepatic cirrhosis in the presence of VN is not precisely

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understood. The renin-angiotensin system is activated by their increased sympathetic activity in VN. Increased AII may thus cause renal failure by impairing the perfusion. The parasympathetic neuropathy may cause an increased of death rate from hemorrhage and sepsis by altering afferent input to the central volume receptors and baroreceptors in cirrhosis (4 - 7).

The defect of parasympathetic innervation in hepatic disease, presents with an increased heart rate at rest and decreased heart rate in respiration periods (inspiration and expiration). However, the defect on sympathetic innervation presents with a decrease in blood pressure when standing up from supine position (6 - 8).

It is difficult to evaluate the autonomic nervous system and symptoms are a poor indication of the possible presence of VN. Symptoms of the disorder such as vertigo, dryness of eyes and/or mouth, dysphagia, abnormal sweating, impotence and constipation are found in many diseases and these are rarely recorded at routine physical examinations. However, Ewing et al. have prepared standardized testing batteries which quantitavely measure heart rate and blood pressure variations during Valsalva maneuver and deep respiratory and postural changes (9,10).

Recently, there have been many reports about the increase in VN, a negative prognostic factor which increases mortality in hepatic cirrhosis. This study was therefore undertaken to evaluate the incidence of VN and its relationship to age, sex, etiology, serum albumin and bilirubin levels and prothrombin time.

MATERIALS AND METHODS

Thirtyfive patients, under treatment at the Internal Medicine Clinics of the SSK Göztepe Educational Hospital, were included in the study. There were 27 male and eight female patients aged between 21 and 70 years (mean 58±11.6 years). Informed consent was obtained from each patient included in the study and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

A diagnosis of hepatic cirrhosis was based upon the following criteria: hepatic biopsy or clinically determined splenomegaly, specific ultrasonographic appearance, laboratory findings of hepatic cirrhosis and the presence of esophageal varices for at least six months. Out of 35 patients, 25 had cirrhosis with chronic viral hepatitis (hepatitis B in 21 and hepatitis C in four patients), four had alcoholic cirrhosis and six had cryptogenic cirrhosis.

The control group comprised 20 healthy voulnteers (15 male, five female) aged between 44 and 71 years, with a mean age of 53.4±8.6 years.

No subject in either the patient or control group had diabetes mellitus, chronic renal failure, thyroid disease, hypertension, neurological disease or serious ECG abnormalities (including blocks and all types of arrythmias) and none of them were taking beta blockers and/or diuretic medication. Alcohol consumption was prohibited from one week prior to commencment of the study.

Clinical evaluation

Patients were questioned about the presence of the following symptoms: tachycardia at rest, syncope, constipation, orthostatic hypotension, urinary and/or rectal incontinence and impotence (in male patients).

The cardiovascular reflex tests used to evaluate vagal functions were as follows:

1- Heart rate at rest: Determination of heart rate increases over 100 beats/minute by monitoring the patient in a supine position for five minutes after 15 minutes of rest.

2- The heart rate response to deep breathing: with the patient in supine position, minimum and maximum heart rates reached during six deep breaths per minute (five seconds of inspiration, five seconds of expiration) were recorded.

3- Heart rate response to Valsalva maneuver: patients prerformed the Valsalva maneuver for 20 seconds in a supine position. The Valsalva ratio was the ratio of the longest R-R interval after the maneuver to the shortest R-R interval during the maneuver, determined by ECG monitoring.

4- Heart rate response to posture change from lying to standing: patients were instructed to rapidly stand up from a supine position. After standing up, each patient was monitored by ECG for one minute. The 30:15 ratio was estimated by measuring the 30th and 15th R-R intervals.

5- Blood pressure response to standing: blood pressure was measured every minute for five minutes with the patient in a supine position and repeated after the patient was instructed to stand up quickly. A 30 mmHg or more decrease in sys-

Table 1. The comparison of vagal neuropathy (VN) and cardiac vagal neuropathy (CVN) in the patient and control groups.

Tests	*Patients (n=35)*	*Controls (n=20)*	*p value*
CVN 1 (+)	5	0	p > 0.05
CVN 2 (+)	19	0	p < 0.001
CVN 3 (+)	20	0	p < 0.001
CVN 4 (+)	19	3	p < 0.05
VN (+)	20	0	p < 0.001

tolic blood pressure was evaluated as hypotension.

Only four of the five cardiovascular reflex tests evaluate vagal functions: the heart rate at rest, the heart rate response to deep breathing, a Valsalva maneuver and the lying-to-standing position. However, the heart rate at rest is a poor indicator of vagal impairment.

The evaluation of cardiovascular reflex tests:

Patients were divided into two groups: the CVN (-) group comprised those with normal tests results or only one test evaluated as suspicious or abnormal, while the CVN (+) group included those with two or more abnormal vagal function tests.

Chi square, Fisher's exact chi square and t-test for independent groups tests were used to evaluate the findings.

RESULTS

Symptoms of VN in patients: 29 of the patients (82.8%) included in the study had one or more of the following symptoms related to VN.

a. Constipation: 18 (51%)

b. Diarrhea: 17 (48%)

c. Nausea – vomiting: 16 (45%)

d. Impotence: 11 (31.4%)

e. Urinary incontinence: 6 (17%)

f. Rectal incontinence: 2 (5.7%)

Responses to cardiovascular reflex tests related to vagal functions:

1. Heart rate at rest: It was found to be abnormal in five (14.3%) and normal in 30 (85.7%) of the 35 patients included in the study. All control group subjects had normal heart rates at rest. There was no significant difference between the control group and the cirrhotic patients' group (p>0.05).

2. Heart rate response to deep breathing: This was found to be abnormal in 19 (54.3%) and normal in 16 (45.7%) of the patients, while all control group subjects had a normal heart rate response to deep breathing. The heart rate response to deep breathing in the cirrhotic patients group was significantly lower than the control group (p<0.001).

3. Heart rate response to Valsalva maneuver: while responses in all control group subjects were normal, they were abnormal in 20 (57.2%) and normal in 15 (42.8%) of the patients group (p<0.001).

4. Heart rate response to lying to standing position: It was abnormal in 19 (54.3%) and normal in 16 (45.7%) of the patients but abnormal in only three (15%) of the control group members (p<0.05).

In summary, VN was determined in 20 (57%) patients, but in no subject in the control group; thus a significant difference was found between groups (p<0.001) (Table 1).

The mean age of cirrhotic patients with VN was 59.5±11 years; while it was 55.9±11.9 years in patients without VN. There was no significant difference between the ages of the patients with and without VN (p>0.05) (Table 2).

Vagal neuropathy was found in four (50%) of eight female and in 16 (59%) of 27 male patients, indicating no significant difference according to gen-

Table 2. The comparison of VN (+) and VN (-) patients according to sex, age and etiology.

		VN (+)	*VN (-)*	*p value*
Sex	Female (n=8)	4 (50%)	4 (50%)	p > 0.05
	Male (n=27)	16 (59%)	11 (41%)	
The mean age (years)		59.5 ± 11	55.9 ± 11.9	p > 0.05
Etiology	Alcohol (n=4)	3 (75%)	1 (25%)	p > 0.05
	Viral hepatitis (n=25)	16 (64%)	9 (36%)	
	Cryptogenic (n=6)	1 (16%)	5 (84%)	

Table 3. The comparison of vagal neuropathy (VN) positive and negative patients according to serum albumin and bilirubin levels and prothrombin time.

	VN (+)	*VN (-)*	*p value*
Albumin	2.77±0.5	3.67±0.66	p > 0.05
Prothrombin time	19.6±1.8	15.5±3.3	p < 0.05
Total Bilirubin	4.07±0.5	2.79±0.3	p < 0.01

der (p>0.05) (Table 2).

Three (75%) of four alcoholic patients with cirrhosis, 16 (75%) of 25 patients with cirrhosis due to viral hepatitis and one (16%) of six patients with cryptogenic cirrhosis had VN. There was no significant difference between the patients with and without VN according to the etiology of cirrhosis (p>0.05) (Table 2).

The mean serum albumin level of cirrhotic patients with VN was 2.77±0.59 g/dl while it was 3.67±0.66 g/dl in cirrhotic patients without VN, thus no significant difference was observed between those with and without VN (p> 0.05) (Table 3). The mean prothrombin time (PT) of cirrhotic patients with VN was significantly longer at 19.6±1.8 seconds while it was 15.5±3.3 seconds in those without VN (p<0.05) (Table 3). The mean serum total bilirubin level was 4.07±0.5 mg/dl in the cirrhotic patients with VN and 2.79±0.3 mg/dl in patients without VN, being significantly higher in cirrhotic patients (p<0.01) (Table3). Of the twenty cirrhotic patients with VN, 11 were in Child B and nine were in Child C stages. No patient with VN was found to be in Child A stage. Of the other 15 cirrhotic patients without VN, four patients were in Child A, 10 were in Child B and one in Child C stage.

DISCUSSION

In this study, the most frequent symptoms of VN were constipation (51%), diarrhea (48%) and nausea-vomiting (45%). Some reports assert that heart rate responses to Valsalva maneuver and to deep breathing are the most sensitive tests among cardiovascular reflex tests and these were also used in our study (9,11,12) where abnormal heart rate responses to Valsalva maneuver were detected in 19 (54.3%) and to deep breathing in 20 (57%) patients. Both of these tests were most frequently positive out of all the tests, which is in accordance with results of other studies (12,13).

Impaired cardiovascular reactivity in patients with chronic liver disease could predispose them to circulatory failure after hemorrhage or surgery (14,15). It has been shown that heart rate and cardiac output increase and peripheral vascular resistence decreases in patients with cirrhosis (16,17). In this study, it was also observed that heart rate (91.1±16.6 beats/minute) and cardiac output (EF=83.3±10.2%) were significantly increased and peripheral vascular resistence significantly decreased (BP=106.9±14.9/59.1±12.3 mmHg) in cirrhotic patients compared to the control group.

To date, no striking relationship between CVN results and sex, etiology and age has been reported (14,18,19), which is in accordance with the findings of this study. (p>0.05). However, a parallel has been seen in former studies between PT, serum albumin and bilirubin levels and the Child-Pugh classification of cirrhosis and VN (4,20,21). This study also found PT to be significantly longer and serum bilirubin levels significantly higher in VN(+) patients with cirrhosis compared to VN(-) patients (p<0.01). However, no significant difference in serum albumin levels was found in patients with and without VN (p>0.05).

If it could be proven that VN is an independent risk factor in cirrhosis without any doubt, then the Child-Pugh classification can be altered to be added that VN is an independent variable (4).

In some clinical studies, hepatic functions of cirrhotic patients with parasympathetic dysfunction have been found to be worse and also their sodium and water excretions were spoiled compared with patients without parasympathetic dysfunction. It has also been determined that sodium and water excretions are more closely linked to results of parasympathetic autonomic tests than parameters of hepatic dysfunction (7,22).

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