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Cardiovascular problems in cirrhotic patients

Sirotik hastalarda kardiyovasküler sorunlar

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Cardiovascular disease associations with chronic liver disease are identified. The effect of these cardiovascular diseases on the natural history of the underlying liver disease is considered. Their recognition and management is important in the long term care ofpatients with chronic liver disease, especially those being considered for liver transplantation.

Keywords: Cirrhosis, arrhythmia, myocardiopathy, hypotension, hyperdynamic syndrome, coronary artery disease

Kronik karaciğer hastalığı ile ilişkili kardiyovasküler hastalıklar tanımlanmıştır. Bunların karaciğer hastalığına etkileri dikkate alınmalıdır. Karaciğer trasplantasyonuna hazırlananlar başta olmak üzere tüm karaciğer hastalıklarında kardiyovasküler hastalıkları iyi araştırılmalıdır.

Anahtar kelimeler: Siroz, aritmi, myokardiyopati, hipotansiyon, hiperdinamik sendrom, kroner arter hastalığı

INTRODUCTION

Cardiovascular disease (CVD) is a common medical problem in adults older than age 40 and is a particularly common problem in those who are 50-60 years of age. Cirrhosis is a hepatic disease process that typically presents in individuals, who are in these same age groups. As a result, CVD is a common co-morbid disease process in individuals with cirrhosis and has important clinical consequences in those who require surgery for any reason (1-7).

CVD process in cirrhotics can occur either as a part of a systemic disease process that involves the liver, a systemic disease process that does not involve the liver per se or as a localized cardiac disease process without associated hepatic or systemic involvement.

I. CVD That Occurs as Part of a Systemic Disease Process that Also Involves the Liver

The classic systemic disease processes that involve both the heart and the liver are hemachromatosis, Wilson's disease and the two glycogen storage diseases that involve the liver. Other systemic disease processes that also affect the liver include amyloidosis, sarcoidosis, AIDS and less after chronic hepatitis B and chronic hepatitis C.

The heart disease in hemachromatosis, Wilson's disease, glycogen storage disease and amyloidosis is characterized initially by a hyperthrophic heart with reduced compliance that can progress to a dilated cardiomyopathy associated with various cardiac arrhythmias.

The hepatic and cirrhotic problems found in patients with these diseases represent components of these systemic disease processes involving the liver and the heart.

Systemic infections such as AIDS and less commonly chronic hepatitis B and C can also involve the heart and produce dilated cardiomyopathies, arrhythmias and pericardial effusions that can occasionally present with tamponade or pericarditis.

II. CVDs That Occur in Cirrhotic Patients That Occur Independent of the Comorbid Hepatic Disease

Atherosclerotic CVD, rheumatic valvular heart disease and particularly coronary artery disease are

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common problems seen in the clinic. As such these diseases also involve cirrhotics. Many patients with liver disease have elevated serum cholesterol and triglyceride levels. Those with far advanced hepatocellular disease often have low levels of cholesterol but have high levels of triglycerides. Despite the low serum cholesterol, coronary artery disease is as common in cirrhotics as it is in the noncirrhotic population and may occur at an even higher rate unless the data are corrected for the comorbid condition of tobacco usage.

These diseases present no differently in cirrhotics as compared to noncirrrhotics with chest pain, angina, myocardial infarction, and congestive heart failure.

III. Myocardial Dysfunction Occurring as a Consequence of the Hepatic Disease Not Associated With a Systemic Disease Process

A) Anatomic / Physiologic changes

Cardiovascular function is frequently impaired in cirrhotic patients and this dysfunction has a direct relationship with the degree of hepatic dysfunction defined by either the Child-Pugh score or the Model for End Stage Liver Disease (MELD) score. This CVD process is characterized by hemodynamic changes termed "the hyperdynamic syndrome" and has been reported to occur in more than 30% of cirrhotics patients (1, 2). The components of this syndrome include an increased cardiac output, increased heart rate, increased vascular volume, reduced arterial pressure, reduced systemic vascular resistance and impaired renal and enhanced visceral perfusion. The hyperdynamic circulatory consequences of this syndrome can lead to morphologic alterations in the heart to include right atrial and right ventricular dilatation (3-5). Left atrial dilatation has been reported also but left ventricular dilatation does not occur presumably as a consequence of the reduced systemic vascular resistance (6). Some investigators have reported increased left ventricular end diastolic and end systolic volumes (7, 8).

The hyperdynamic circulatory state occurring in cirrhotics was initially identified in individuals with alcoholic cirrhosis. As a result, it was initially confused with alcohol induced cardiomyopathy. However, with its recognition in cirrhotics with etiologies distinct from alcohol abuse and its occurrence in patients with extrahepatic portal hypertension in the absence of hepatic disease, it has been recognized as a CVD associated with portal hypertension and not hepatic disease per se.

Experimental data obtained in animals and to a lesser degree in man has shown that an excess production of nitric oxide resulting in increased nitric oxide levels in plasma plays a major role in the initiation and maintenance of the hyperdynamic state of the cirrhotic patient (10, 11). Nitric oxide however, is not the sole factor responsible for the hyperdynamic state. Other factors such as increased levels of endotoxin, tumor necrosis factor, bile acids, glucagon and others in the plasma contribute to the phenomenon. The increase in these later substances is generally not a result of increased production as is the case with nitric oxide but rather occurs as a consequence of a reduced hepatic clearance of these factors (12, 13).

At the level of the myocardial cell, reduced levels of adrenergic receptors and other myocardial membranous abnormalities have been documented as part of this syndrome and impair the cardiovascular response to sympathetic nervous system stimulation and as a result contribute to the overall myocardial dysfunction seen in this syndrome (14, 16). Very late in the natural history of portal hypertension and the heart disease associated with it, the absolute increased blood volume occurring in cirrhotics with portal hypertension can lead to left ventricular volume overload, left ventricular dilation and pulmonary congestion as a consequence of left heart failure (17).

In compensated cirrhotics, the hyperdynamic syndrome and resulting cardiac dysfunction is either absent or clinically mild as a consequence of the reduced systemic vascular resistance. This situation can change rapidly however if these patients are challenged by a pharmacologic stress (dobutamine or other adrenergic agonist) (6, 18) or a physiologic cardiovascular stress such as exercise, the postprandial state, infection, bleeding and even mental stress (8, 14, 19-21).

Cirrhotic individuals have normal to increased left ventricular ejection fractions at rest. Under stress however, the left ventricular ejection fraction can either increase further or actually decline. When it increases, the increase is typically less than that seen in normal individuals. This failure to increase the left ventricular ejection fraction with stress is caused by a combination of a blunted heart rate response to adrenergic stimuli and a reduced myocardial contractility (22).

Procedures that reduce portal hypertension such as surgical portal caval shunts, transjugular intrahepatic portosystemic shunts (TIPS) and liver transplantation can partially ameliorate the hyperdynamic syndrome but can also be complicated by pulmonary edema and right heart failure as a consequence of a markedly increased venous return that overwhelms the left atrium and the right atrium and ventricle (24-26).

In patients with massive ascites, cardiac function

can be impaired further as a consequence of a displacement of the diaphragm upward increasing intrathoracic pressure (reducing the reduction of intrathoracic pressure that occurs with respiration) and can impair right atrial and right ventricular compliance resulting in reduced filling and diastolic dysfunction of the right side of the heart. In these patients, a paracentesis enhances cardiac function by increasing right heart compliance and increasing the right ventricular ejection fraction (27). As a result, patients with massive ascites undergoing a TIPS or a portal systemic shunt should undergo a therapeutic paracentesis prior to the planned procedure to minimize the acute adverse effects of these procedures on heart function. A dobutamine stress test or equivalent test prior to the procedure in such cases can identify individuals at particularly high risk for cardiac decompensation following one of these procedures.

Serum troponin I levels, a specific marker of myocardial injury are reported to be elevated in 32% of patients with cirrhosis (29). Both subclinical ventricular myocardial injury and strain have been suggested as a cause of this phenomenon (30). It is important to note however that these increases in troponin I levels occurs in the absence of increases in creatine kinase. This suggests that the troponin I levels are increased in the absence of myocardial cell plasma membrane injury and represent a stress rather than injury related response. This also suggests that any additional cardiac stress in cirrhotics with elevated troponin I levels could lead to myocardial failure.

B) Myocardial membrane changes

The fluidity of myocardial cell membranes is altered in cirrhotics. Moreover, several transmembrane plasma membrane ion channels have been shown to be dysfunctional both in cirrhotic men and cirrhotic animals (31-34). Specifically K+ and Ca+2 channels in myocardial and vascular smooth muscle cells of cirrhotic individuals and animals have been shown to be abnormal and these changes have been suggested as being a cause of the altered systemic vascular tone found in cirrhotics (32, 33). As a consequence of these ion channel alterations in cardiac membranes, it is not unexpected to find electrophysiologic alterations in these same cells that might contribute to enhanced myocardial excitability. One of the more common and clinically important electrophysiologic changes reported in cirrhotics is a prolongation of the QT interval detected by electrocardiography (EKG) (35-39). This interval is a measure of the time from the earliest activation (depolarization) of myocardial cells to the end of ventricular repolarization. A prolongation of the QT can occur either as a congenital abnormality (40) or be acquired. Some of the recognized causes of an acquired prolonged QT are shown in (Table 1).

Women have longer QT intervals than do males. The QT interval is affected by heart rate and the corrected QT interval (QTc) is the QT interval corrected for the heart rate. A prolonged QTc can occur as a consequence of slowed progressive depolarization or prolongation of the repolarization process. A QTc interval > 0.440msec is a well recognized risk factor for serious ventricular arrhythmias and a potential for sudden death.

Table 1. Acquired causes of prolonged QTc

Cardiac disease (especially myocardial ischemia)
Electrolyte abnormalities (hypokalemia, hypocalcemia, hypomagnesemia)
Drugs (cisapride, phenothiazines, erythromycin, trimethoprim-sulfamethoxazole, vasopressin, pentamidine, tricyclic antidepressants, quinidine)
Alcohol
Autonomic nervous system disturbances
Abnormalities in gonadal hormone metabolism
Hypercholalemia

QTc prolongation has been reported to occur in 37-84% of cirrhotic individuals with either alcoholic or nonalcoholic liver disease (48-54). Table 2 identifies the frequency of QTc interval prolongation in individuals with advanced liver disease reported by various investigators.

The specific mechanisms responsible for QT prolongation in cirrhotics are controversial. Several investigators have shown a relationship between disease severity as defined by the Child-Pugh score that occurs independently of the specific disease etiology. Moreover, some have reported an independent effect of the QTc on mortality (37). Bernardi et al. reported a direct correlation between plasma noradrenalin levels and the QTc suggesting that enhanced adrenergic stimulation of myocardial cells plays a role in pathologic electrophysiology defined as a prolonged QTc (58, 59). This conclusion is reinforced by the observation that autonomic neuropathies can be a cause of a prolonged QTc (60, 61) and neural mechanisms influence ventricular depolarization and repolarization

Table 2. Prevalance of QT prolongation in cirrhotic patients

	Prevalance%
Singh Bal	40
Puthumana	45
Henriksen	37
Bernardi	47
Mohamed	83

Table 3. Prevalance of autonomic neuropathy in patients with cirrhosis

	Prevalence of Autonomic Neuropathy
Bernardi	80
Puthumana	79
Perez-Penaa	68
Kempler	82
Mohamed	79

phenomena. Despite this, potential for liver disease severity and autonomic dysfunction to collectively contribute to the prolonged QTc interval noted in cirrhotic individuals; Puthumana et al have reported that the prolonged QTc in cirrhotics occurs independently of any autonomic dysfunction (51). Nonetheless, it is important to note that autonomic dysfunction and a prolonged QTc are both common in cirrhotics (Table 3). Fortunately for clinicians, most of the cirrhotic individuals with autonomic neuropathy are asymptomatic.

The pathogenesis of the autonomic neuropathy seen in cirrhotics is unclear. Immunologic, toxic, alcohol, vitamin E deficiency, abnormalities of lipid metabolism, increased levels of angiotensin II and neurotransmitter abnormalities affecting nerve cell integrity have been suggested. The autonomic dysfunction in cirrhotics have been shown to correlate with the degree of hepatic disease and improves following successful liver transplantation suggesting that reduced hepatic clearance of potential neurotoxins is a potential cause of the neuropathy (49, 53, 60, 71). The effect of a recognized autonomic neuropathy on the mortality of cirrhotic patients is controversial with some investigators reporting an increased mortality rate in cirrhotics with autonomic neuropathy with others disputing this finding (49, 51, 53, 69, 71).

The torsade de pointes phenomenon is an uncommon but well recognized arrhythmia in the context of an underlying prolonged QTc interval. The ventricular rate in such cases can vary between 150-250 beats/min and last for 5- 15s with longer episodes progressing to overt ventricular fibrillation and sudden death. Importantly, sudden death is not common in cirrhotics but cirhotics with prolonged QT intervals may be at risk for sudden death when they experience a major stress response as occurs in cases of massive gastrointestinal bleeding, overwhelming sepsis or during or after major abdominal surgery.

Many of the drugs prescribed for cirrhotics have been shown to affect the QTc interval (Table 4). Because of the high rate of prolonged QT intervals reported in cirrhotics, these drugs should be prescribed cautiously, after a baseline EKG has been obtained and their effect on the QT interval noted with follow-up EKGs.

C) Pericardial effusions

The fluid retention that occurs in cirrhotic can lead to the development of ascites, hydrothorax, anasarca and a pericardial effusion. The prevalence of the later ranges from 32 to 63% depending upon methods used to identify the abnormality (73-75). The presence of a pericardial effusion occurs only in those with advanced liver disease typically those with overt liver failure and anasarca. The principle treatment of a pericardial effusion in a cirrhotic is treatment directed at a diminution of fluid retention, specifically therapy for ascites. Pericardial tamponade as a consequence of pericardial effusion in a cirrhotic is unusual but can occur and has been reported in cases of hepatitis C infection and following a TIPS procedure. In these cases, immediate pericardiocentesis is required followed in some cases with creation of a pericardial window. The later can be accomplished with or without thoracic surgery with the former course being utilized more frequently given its relatively recent introduction into clinical practice of the later method.

D) Coronary artery disease (CAD)

The frequency of CAD has been recognized for years to be reduced in cirrhotic patients with hepatocellular disease primarily related to alcohol abuse (76, 77). This finding has been explained in part by the reduced serum levels of cholesterol seen in such subjects and has been documented by several

Table 4. The Drugs That Prolong the QTc Interval

	Drugs Discontinued from Marketing Due to QTc Effect	Other Drugs That Prolong the QTc Interval
Antihistamine	Terfenadine, Astemizole	
Central Nervous System	Sertindole, Droperidol	Ziprasadone, Thioridazine, Risperidone
Antibiotic	Grepafloxacin	Erythromycin Clarithromycin, Ketoconazole, Fluconazole, Moxifloxacin, Trimethoprim-Sulfamethoxazole
Gastro-Intestinal	Cisapride	
Genito-Urinary	Terodiline	
Antiarrhythmic		Quinidine, Sotalol, Amiodarone
Anti-rejection		Tacrolimus
Neoplastic Agents		Arsenic, Tamoxifen

autopsy studies (78). The recognition of the hyperdynamic cardiac syndrome that occurs in cirrhotics has been recognized also as a potential cause of a reduced frequency of CAD in cirrhotics as a consequence of systemic vasodilatation, a reduced systemic vascular resistance and relative hypotension (76-77, 79-80). In addition, the observation that mild to moderate alcohol consumption is associated with increased levels of high-density lipoproteins has reinforced this observation at least in alcohol users (82, 83). Finally, males with advanced liver disease particularly cirrhosis are often feminized as a consequence of a reduced plasma androgen to estrogen ratio. This relative increase in plasma estrogen in suspected as contributing to the reduced vascular disease reported in cirrhotics (81).

Despite these many studies, the relatively recent introduction of liver transplantation into clinical practice has documented that cirrhotic individuals particularly those with nonalcoholic liver disease (HCV and cholestatic liver disease), have a higher rate of CAD that had been expected based upon the earlier autopsy and clinical observation made almost exclusively in the alcoholic population (84-90). Plotkin et al. reported a higher rate of cardiac morbidity and mortality in cirrhotic patients with angiographic evidence of CAD than in those without such findings (86-89). Thus, the current rule in many liver transplant centers is to require a cardiac stress test particularly a dobutamine stress test with combined EKG and echocardiographic monitoring prior to transplant listing (86, 87, 91-94). Moreover, as a result of this practice, cirrhotics are being subjected to coronary angiography, coronary artery angioplasty or stenting and even cardiac bypass procedures more often than has been the rule in the past.

In addition, the recommendations of the American Heart Association consensus panel on risk reduction in patients with CAD should become routine measures in cirrhotic patients particularly those being considered for liver transplantation. Briefly, those suggestions could be made:

-Patients should stop smoking,

-Aggressive lipid management, targeting of low-density lipoprotein levels < 100 mg/dL. (pay special attention to hepatotoxicity while these patients are on lipid-reducing medications),

-If possible, physical activity and weight control is advised,

-Aggressive management of diabetes, targeting hemoglobin Ale < 7%,

-Blood pressure control (beta-blocker could be considered in patients with portal hypertension and varices; low-dose angiotensin-converting enzyme inhibitors could be considered in patients who have had a myocardial infarction and have left ventricular dysfunction, with close monitoring of renal function).

IV. SUMMARY

Almost one third of cirrhotic patients can be shown to have evidence for a myocardiopathy. Both systolic and diastolic blood pressure levels are abnormal in cirrhotics and parallel the degree of liver dysfunction. Special attention needs to be directed at the detection of a prolonged QT interval and its worsening with the use of drugs known to increase the QT interval particularly those used commonly in cirrhotics. Although CAD occurs less often in cirrhotics than in the general population, it does occur in cirrhotics and adversely affects liver transplant outcome. Pericardial effusions can occur in cirrhotics as a consequence of an overall defect in fluid and electrolyte to regulation.

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