CARDIOVASCULAR DISEASE CAUSED BY HEPATIC CIRRHOSIS – CIRRHOTIC CARDIOMYOPATHY

LORENA MĂRIEŞ[1], I. MANIŢIU[2]

[1]PhD candidate „Lucian Blaga" University of Sibiu, [2]„Lucian Blaga" University of Sibiu

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Abstract: *Hepatic cirrhosis is associated with a series of cardiovascular abnormalities including hyperdynamic circulation, portal hypertension, hepatopulmonary syndrome and modifications within other vascular areas, such as the renal and cerebral ones. In the recent years, we have noticed that invasive procedures performed on cirrhotic patients, such as the transjugular intrahepatic portosystemic shunt (TIPS) or the liver transplant, are associated with a high mortality rate. Although these procedures represent a cardiovascular challenge, a normal heart should easily adjust. The heart's inability to adjust has represented an indication for cirrhotic cardiomyopathy.*

Cuvinte cheie: *cardiomiopatie cirotică, ciroză hepatică, TIPS*

Rezumat: *Ciroza hepatică este asociată cu o serie de anormalităţi cardiovasculare ce includ circulaţie hiperdinamică, hipertensiune portală, sindrom hepatopulmonar şi modificări în alte teritorii vasculare precum cel renal si cerebral. În ultimii ani, s-a observat că, manevre invazive efectuate la pacienţii cirotici, ca şuntul transjugular intrahepatic portosistemic (TIPS) sau transplantul hepatic, se asociază cu o mortalitate ridicată. Chiar dacă aceste manevre reprezintă o provocare cardiovasculară, inima normală ar trebui să se acomodeze uşor. Incapacitatea inimii de a se acomoda a reprezentat un indiciu al existenţei cardiomiopatiei cirotice.*

The liver and the heart being directly interconnected at vascular level (by means of the suprahepatic veins and the inferior vena cava), the primary disease of either of them will cause the secondary disease of the other. Whereas hepatic disease caused by heart failure is well documented, with popular terms such as "cardiac cirrhosis" or "cardiac liver", the same does not apply to the heart disease caused by hepatic cirrhosis, the new clinical entity, called "cirrhotic cardiomyopathy", being less familiar. The transjugular intrahepatic portosystemic shunt (TIPS) has become even more popular in the recent years, as a non-surgical approach of treating resilient ascites or variceal bleedings in the case of cirrhotic patients.(1) It represents a cardiovascular challenge since it suddenly relocates a large amount of venous splanchnic blood into the systemic circulation, which means a preload increase. Unsurprisingly, this procedure, performed almost invariably in the case of patients with advanced liver failure is associated to a high mortality rate.(1)

The normal heart should easily adjust to a slight up to a moderate increase of the preload, induced by the TIPS. The inability of the heart to adjust indicates the existence of cirrhotic cardiomyopathy. This cardiomyopathy may also determine the final result in cases of liver transplant. 30 to 35 years ago, several studies of the cardiac function conducted on patients with alcoholic cirrhosis have shown a decrease of the ventricular response to stimuli such as medication or physical effort, which the authors attributed to a slight alcoholic cardiomyopathy. During the '80s, a change in attitude took place when several studies conducted on animal models with non-alcoholic cirrhosis displayed the same low response to stimuli. Subsequently, studies on patients with non-alcoholic cirrhosis demonstrated the fact that these modifications are visible with all forms of cirrhosis. Therefore, this basal hypercontractility phenomenon, with a low contractile ventricular response to physiological or pathological stimuli is called cirrhotic cardiomyopathy.(2)

The definition of cirrhotic cardiomyopathy:

The term of cirrhotic cardiomyopathy is currently defined as:

1. elevated cardiac flow at rest, but a low ventricular response to stimuli;
2. systolic and/or diastolic dysfunction;
3. absence of an obvious left ventricular failure at rest;
4. electrophysiological abnormalities such as a prolonged QT interval and chronotropic incompetence.

Not all of the above are necessary to put a diagnosis; for instance, only 30-60% of patients display a prolonged QT interval.(3) On the other hand, cirrhotic cardiomyopathy includes modifications such as: the decrease of the function of beta adrenergic receptors, the dysfunction of post-receptors and the defective excitation-contraction coupling.(4)

Epidemiology:

In the absence of clearly defined diagnostic criteria, the accurate prevalence of cirrhotic cardiomyopathy remains unknown. Equally, its estimation is a difficult task since the disease is generally latent and stands out only when the patient is subjected to stress, such as changing one's body position, physical exercise, medication, haemorrhage or surgical procedure. Moreover, the prevalence of hepatic cirrhosis is difficult to estimate since numerous individuals with compensated cirrhosis do not show symptoms or indications of the disease and non-invasive examinations lack the sensitivity in detecting cirrhosis in its early stages.(3)

Etiopathogenesis:

There is no direct genetic predisposition for cirrhotic cardiomyopathy. The pathogenic mechanisms include the malfunctioning behaviour of signalling paths of the β-

[1] Corresponding author: Lorena Mărieş, Str. Dîrstelor, Nr.15, Sibiu, România; e-mail: lorenamaries@yahoo.com; tel +40745387973
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adrenergic receptors, the alteration of the physical and chemical properties of the cardiomyocytes' membrane and the hyperactivity of negative inotropic factors such as nitric oxide, carbon monoxide and the endocannabinoid systems.(3)

Clinical features:

Numerous aspects of the cardiac contraction have been described as abnormal in cases of cirrhosis, including the systolic and diastolic function. Functional and structural modifications of the cardiac chambers have been noticed more frequently in the left half of the heart than in the right one. Most studies found a dilation of the left atrium, as well as a dilation or hypertrophy of the left ventricle. The right atrium and ventricle generally have normal sizes in the absence of the unusual portopulmonary hypertension syndrome.(3)

The prevalence and the extent in which the systolic dysfunction occurs are variable in the case of cirrhotic patients. By contrast, the diastolic dysfunction seems to be a lot more common. It appears that a degree of diastolic dysfunction is present with all cirrhotic patients. This dysfunction manifests itself in the form of a rigid, noncompliant ventricle, and is often noticed in the case of patients with a certain degree of left ventricular hypertrophy or dilation.(3)

Electrophysiological modifications, including prolonged repolarization and the defective excitation-contraction coupling have been demonstrated in cirrhotic patients. The prolonged repolarization manifests itself in the form of a prolonged QT interval on the electrocardiogram. This prolongation of the QT interval may be associated to an elevated risk of ventricular arrhythmia, the torsade de pointes in particular.

The visible heart failure is rare due to the peripheral vasodilation characteristic to cirrhosis, which has the effect of "self-treating" the ventricle, the systemic vasodilation reducing the preload and diminishing in a compensating manner the inhibitory influences such as the muscarinic cardiac system. Although patients may complain of dyspnoea, low physical effort capacity, peripheral retention of fluids and ascites, these symptoms are common in heart failure and advanced cirrhosis.

Stress factors such as the liver transplant, infections and procedures such as the insertion of a transjugular intrahepatic portosystemic shunt (TIPS), may convert a latent heart failure into a visible one. Heart failure accounts for 7-15% of the post-liver transplant mortality rate and, in certain cases it is the third mortality cause after transplant rejection and infection. Numerous studies have reported an acute left ventricular failure or more subtle indications of heart failure after the liver transplant, even in the case of patients with no cardiac history and or risk factors. All these suggest that cirrhotic cardiomyopathy is the main determining survival factor for cirrhotic patients undergoing various procedures which stress the cardiovascular system.

Paraclinical laboratory tests:

Cirrhotic cardiomyopathy may be diagnosed by using a combination between electrocardiogram, bidimensional echocardiography and serum markers, such as B- type natriuretic peptide.(5) In addition to the above, due to simultaneous pulmonary complications, its increased reliability and capacity of providing a comprehensive cardio-pulmonary image, a chest x-ray may be added.

Three electrophysiological anomalies have been noticed in the case of cirrhosis, regardless of its etiology: the QT interval prolongation, chronotropic incompetence and electromagnetic dissynchronism. The mechanism leading to the QT interval prolongation in cirrhosis is unknown. Many studies suggest that the chronic activation of the sympathetic nervous system (SNS) occurring in cirrhosis plays an important part in the genesis of prolonging this interval.(6)

The autonomous dysfunction is very frequent in the case of cirrhotic patients and features a relatively low parasympathetic activity and an elevated sympathetic tone.(7) The lack of coupling excitation with contraction occurs regardless of the cirrhosis etiology and is more visible in the case of patients with advanced cirrhosis than in those with compensated cirrhosis.(6)

In addition to the electric anomalies, cirrhotic cardiomyopathy also features an increased contractility of the left ventricle at rest and a reduction of the systolic contraction or of the diastolic relaxation regarding the pharmacological, physiological or surgical stress.(8)

At echocardiography, at rest, when the postload is low, cardiac stresses are almost normal and may thus hide an underlying ventricular dysfunction. Thus, heart failure becomes visible only under hemodynamic stress conditions. Therefore, after physical exercise, the end-diastolic pressure in the left ventricle increases, but the expected increase of the cardiac index and the left ventricle ejection fraction is either absent or below the normal values.(9)

Additionally, numerous studies have demonstrated a low E/A ratio in the case of cirrhotic patients. In many situations, the diastolic dysfunction precedes the systolic one, which tends to stand out only under stressful conditions.(8) It has been recently demonstrated that liver transplant leads to a revival of the cardiac functions, including the disappearance of the diastolic dysfunction.(9)

Lately, in addition to the "classic" tests meant to diagnose heart failure, focus was laid on determining the serum markers, under the belief that these have a higher sensitivity and specificity. Among these, mention should be made of the BNP and the NT-pro-BNP.

Numerous recent studies have revealed that patients affected by hepatic cirrhosis have elevated plasmatic concentrations of BNP and NT-pro-BNP, representing, in fact, markers of early ventricular dysfunction. Henriksen et al. have shown that these markers correlate both with the gravity of the hepatic cirrhosis, as well as with that of the heart dysfunction. BNP may thus have a prognostic value regarding the progress of the cirrhosis. Moreover, NT-pro-BNP represents a useful marker in trying to demonstrate the existence of a diastolic dysfunction of the left ventricle, determined by a chronic hepatic disease.(10)

Conclusions:

Should the diagnosis of the congestive heart failure still be a difficult one, the diagnosis of cirrhotic cardiomyopathy, respectively of cardiac dysfunctions in the case of patients without a visible cardiac disease, is even more difficult. For that reason, recognizing the role of the B-type natriuretic peptide, as an objective marker for diagnosis, gravity and prognostic of congestive cardiac failure, has represented a genuine discovery for the medical specialists and patients faced with the cardiovascular disease.(11)

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