MUSCLE CRAMPS IN PATIENTS WITH CHRONIC LIVER DISEASES AND FACTORS ASSOCIATED WITH THEIR DEVELOPMENT

Thesis

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SUMMARY

Chronic liver disease leads to a broad range of systemic manifestations; muscle cramps are one of those manifestations. Muscle cramps adversely affect the quality of life in humans and its pathophysiology has not yet been clearly revealed.

Muscle cramps occur frequently in individual with cirrhosis. We found that about 94% of chronic liver disease with muscle cramps has hepatitis C virus.

Our aim in this study was to determine the prevalence of muscle cramps in patients with chronic liver diseases and to identify factors associated with their development.

In our study 240 subjects were included and classified into 3 groups; group I included 200 HCV patients with chronic liver disease, group II included 20 patients with congestive heart failure, group III included 20 apparent healthy controls.

All included patients were subjected to full history taking, thorough clinical examination and laboratory investigations including complete blood count, liver function tests, renal function tests, viral markers and pelvi-abdominal ultrasound.

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INTRODUCTION

Muscle cramps are a common complaint in clinical practice. They are associated with various metabolic, endocrine, neurological and electrolyte abnormalities ***(Marotta et al., 2000).***

Muscle cramps are a common and recurring symptom in patients with cirrhosis. Although, the pathophysiology has not been specifically studied in cirrhosis, this is thought to be the same for cramps in general, originating in the motor neurons. However, precise pathophysiological mechanisms are not known ***(Corbani et al., 2008).*** Neither biochemical characteristics nor the use of diuretics explained the greater prevalence of cramps in patients with cirrhosis. It is thought that effect of cirrhosis on muscle fibers may be the major factor ***(Baskol et al., 2004).***

Abrams et al. (1996) found that muscle cramps are frequent (52%) in patients with cirrhosis as compared to patients with chronic hepatitis (7.5%) or congestive heart failure (20%) on similar dose of diuretic.

Muscle cramps were more frequent in patients with low albumin, but diuretic use did not predict muscle cramps ***(Abrams et al., 1996).*** Best predictors were the presence of ascites and plasma renin activity ***(Angeli et al., 1996).***

AIM OF THE WORK

To determine the prevalence of muscle cramps in patients with chronic liver diseases and to identify factors associated with their development.

CHRONIC LIVER DISEASES

Definition

Chronic liver diseases describe persistent inflammation of the liver for 6 months or more after initial exposure and/or initial detection of liver disease ***(Dove and Wright, 2004)***.

Causes of Chronic Liver disease

According to ***Thomas et al. (2001)***, there are 4 main causes of chronic liver diseases.

I. Persistent viral infection

1- Hepatitis C:

Transmitted parenterally, following infected blood transfusion and IV drug abuse. 50% of acute infection leads to chronic infection, 10% of that having cirrhosis (with or without HCC) ***(Thomas et al., 2001)***.

2- Hepatitis B:

Infection is mainly by I.V. drug abuse, vertical transmission, blood product, and sexual transmission. In 90% of the patients infected, immune response results in the elimination of the virus but in some cases, chronic infection can lead to cirrhosis and liver carcinoma (HCC) ***(Thomas et al., 2001)***.

II. Auto immune liver disease

1- Auto immune (lupoid) hepatitis:

Commonly seen in females, histologically classified by appearance of chronic active hepatitis dominated by numerous plasma cells and swollen liver cell arranged in rosette-like forms, auto antibodies to smooth muscle antigens are often present ***(Thomas et al., 2001)***.

2- Primary biliary cirrhosis:

Chronic disorders affect mainly middle-aged females. Liver biopsy shows bile duct obstruction, granulomas, ductular proliferation, fibrosis and eventual cirrhosis ***(Thomas et al., 2001)***.

III. Drugs and alcohol

Alcohol liver injury:

Ethyl alcohol is a common cause of acute and chronic liver injury. Alcohol is directly cytotoxic at high concentration, injuring hepatocytes and causing inflammatory reaction. In addition, alcohol stimulates collagen synthesis and leads to fibrosis and cirrhosis ***(Thomas et al., 2001).***

IV. Metabolic disorders

1- Alpha 1-antitrypsin deficiency:

Congenital defects of synthesis, with hyaline globular inclusion in liver. Patients have increased risk of emphysema and cirrhosis ***(Thomas et al., 2001)***.

2-Wilson's disease:

It is an inherited disorder of copper metabolism. Copper accumulate in liver and brain, also causes kayser-fleischer rings at the corneal limbus, low serum caeruloplasmin (a copper containing protein) ***(Thomas et al., 2001)***.

3- Hemochromtosis:

It is an inherited as autosomal recessive disorder. Iron absorption is inappropriately high for dietary intake thereby leading to progressive accumulation of storage iron, iron deposit primarily in hepatecytes as ferritin and subsequently also as hemosiderin with a decreasing gradient of iron deposition from peripheral (zone 1) to pericentral (zone 3) hepatocyte ***(Thomas et al., 2001)***.

Other causes of CLD:

- Secondary biliary cirrhosis.
- Granulomatous disease (e.g. Sarcoidosis).
- Type IV glycogen storage disease.

- Drug-induced liver disease (e.g, methotrextate, alpha methyl-dopa, amiodarone).
- Venous outflow obstruction (e.g, Budd-chiari syndrome, veno-occlusive disease).
- Chronic right sided heart failure.
- Tricuspid regurgitation.

(Wolf, 2005)

Histological Grading and Staging

A standardized scale for the interpretation of histology in chronic hepatitis was developed by ***Batts and Ludwig (1995)***. The grading scale measures the necroinflammatory process; the staging scale measures the degree of fibrosis (Table 1 & 2)

Table (1): *Grading of disease activity in chronic hepatitis:*

Grade	Descriptive	Lymphocytic piecemeal necrosis	Lobular inflammation and necrosis
0	Portal inflammation	None	None
1	Minimal	Minimal, patchy	Minimal, occasional spotty necrosis.
2	Mild	Mild, involving some or all portal tracts	Mild, little hepatocellular damage
3	Moderate	Moderate	Moderate, with noticeable hepatocellular damage
4	Severe	Severe	Severe, with prominent diffuse, hepatocellular damage

(Dove and Wright, 2004)

Table (2): Stages of chronic hepatitis:

Stage	Descriptive	Criteria
0	No fibrosis	Normal connective tissue
1	Portal fibrosis	Fibrous portal expansion
2	Periportal fibrosis	Periportal or rare portal-portal septa
3	Septal fibrosis	Fibrous septa with architectural distortion, on obvious cirrhosis
4	Cirrhosis	Cirrhosis

(Dove and Wright, 2004)

Chronic liver diseases generally progress slowly from hepatitis to cirrhosis, often over 20 to 40 years. Some forms of liver diseases are non progressive or only slowly progressive. Other, more severe forms are associated with scarring and architectural disorganization, which, if advanced, lead to cirrhosis ***(Thomas et al., 2001)***.

LIVER CIRRHOSIS

Definition:

Cirrhosis represents an irreversible state of chronic liver injury. Cirrhosis is defined as fibrosis of the liver with the formation of regenerative nodules. Once a liver has been scarred to the point of cirrhosis, it will probably never return to normal (Figure 1) ***(Sandowski, 2000)***. It can be

also defined as a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal modules that lack normal lobular organization ***(Cheney et al., 2004).***

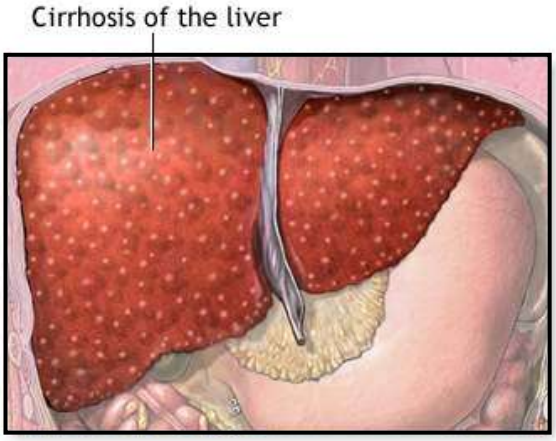

Figure (1): Cirrhosis of the liver

Cirrhosis is a final common pathway of chronic injury, in which viable hepatocytes are replaced with connective tissue. The increasing resistance to blood flow through the liver regularly leads to portal hypertension and its sequel, loss of functional mass leads to impaired synthetic function, abnormal metabolism of the drugs, and poor excretory function ***(Sandowski, 2000)***.

Classification of Cirrhosis

1-Morphological classification: less useful because of considerable overlap (Figure 2).

a- Micronodular cirrhosis. Uniform nodule < 3 mm in diameter: causes include alcohol, hemochromatosis, biliary obstruction, hepatic venous outflow obstruction, jejunoileal bypass, indian childhood cirrhosis.

b- Macronodular cirrhosis. Nodular variation > 3 mm in diameter: causes include chronic hepatitis C, chronic hepatitis B, alpha -1 antitrypsin deficiency, primary biliary cirrhosis.

c- Mixed cirrhosis. It is a combination of micronodular and macronodular cirrhosis. Micronodular cirrhosis frequently evolves into macronodular cirrhosis ***(Anthony et al., 1978).***

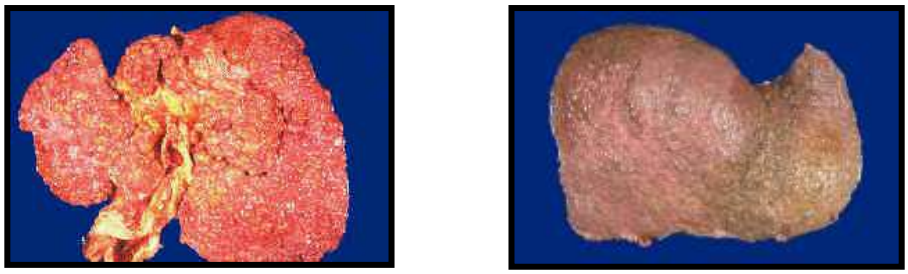

Figure (2): Macronodular cirrhosis & Micronodular cirrhosis

2- Etiologic classification:

- This method of classification is the most useful clinically, by combining clinical, biochemical, histologic, and epidemiologic data; the likely etiologic agent can be ascertained.