Evaluation of Hyperzincuria in Patients with Necrolytic Acral Erythema

Thesis
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ABSTRACT

Necrolyticacral erythema (NAE) was first described in 1996 by El-Darouti and Abou El Ela, it was presented as a cutaneous marker for hepatitis C virus infection.Several pathogenic mechanisms for NAE were postulated. NAE appears to be an immunemediated response in chronic HCV patients, associated with, lower C3 and C4 (complements C3 and C4). Another postulated theory is low serum zinc levels. Hypozincemia and hyperzincuria have been seen in patients with chronic liver diseases due to impairment of protein metabolism which affects the plasma transport of zinc. This study was toevaluate urinary zinc level in patients with necrolyticacral erythema.The mean serum zinc for all patients was lower than the normal reference range and also was lower than that of both HCV-infected control patients group and healthy control group.As regards urinary zinc,its level was in the normal reference range although higher than that of both HCV-infected control patients group and healthy control group but this was not statistically significant.Further studies on the pathogenic mechanisms of the development of NAE was recommended.

INTRODUCTION

Hepatitis C virus (HCV) infection is increasingly reported worldwide with especially high prevalence in the Egyptian population **(Frank et al., 2000).**

HCV infection is often asymptomatic, but numerous extrahepatic disorders, especially dermatological diseases, have been recognized in association with HCV infection **(Jackson, 2002).** Lichen planus, mixed cryoglobulinaemia, porphyria cutanea tarda, prurigo and necrotizing vasculitis have been associated with HCV infection **(Arrieta et al., 2000).**

El Darouti and Abu El Ela (1996) described NAE in 1996 in Egypt·Furthermore, two studies have observed a correlation between severity of HCV infection (based on liver enzymes) and the severity of NAE **(El Darouti et al, 1996 and Nofal et al, 2005).**

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Although several theories were put as regards pathogenesis of NAE, its exact underlying mechanism is not yet settled.

Decreased serum zinc level was suggested as one of these mechanisms **(Abdallah et al., 2004; Hivnor et al., 2004; El-Ghandour et al., 2006).**

It has been postulated that localized cutaneous zinc deficiency may be present in the acral skin of affected patients even when serum zinc levels remain in the normal range, providing a potential explanation for the efficacy of zinc supplementation in patients with normal serum levels of zinc **(Tabibian et al., 2010; Moneib et al., 2010).**

A case reported by **Najarian et al. (2008)** showed hypozincemia and hyperzincuria in a patient with NAE, a finding that had not been reported in other NAE patients.

Hypozincemia and hyperzincuria have also been seen in patients with chronic liver diseases from other etiologies due to impairment of protein metabolism which affect the plasma transport of zinc **(Gusau et al., 1990).**

The case reported by **Najarian et al. (2008)** suggests a possible association between hyperzincuria and NAE which have not been looked for in previous studies.

AIM OF THE WORK

This study aims to evaluate urine zinc level in patients with necrolytic acral erythema

1.0.0. VIROLOGY OF HEPATITIS C VIRUS

1.1.0. Introduction

HCV is one of the Flaviviridae family. The Flaviviridae family includes pestiviruses, flaviviruses and hepacivirus, the only member of hepacivirus is HCV **(Ray et al., 2009).**

1.2.0. Epidemiology

It is estimated that 130–200 million people, or ~3% of the world's population are living with chronic hepatitis C, about 3–4 million people are infected per year, and more than 350,000 people die yearly from hepatitis C-related diseases. Rates have increased substantially in the 20th century due to intravenous medication or poorly sterilized medical equipment **(Ryan and Ray, 2004).**

1.3.0. Structure of HCV

The hepatitis C virus particle consists of a core of genetic material (RNA), surrounded by an icosahedral protective shell of protein, and further encased in a lipid (fatty) envelope of cellular origin. Two viral envelope glycoproteins, E1 and E2 are embedded in the lipid envelope (Fig.1) (**Op De Beeck and Dubuisson, 2003).**

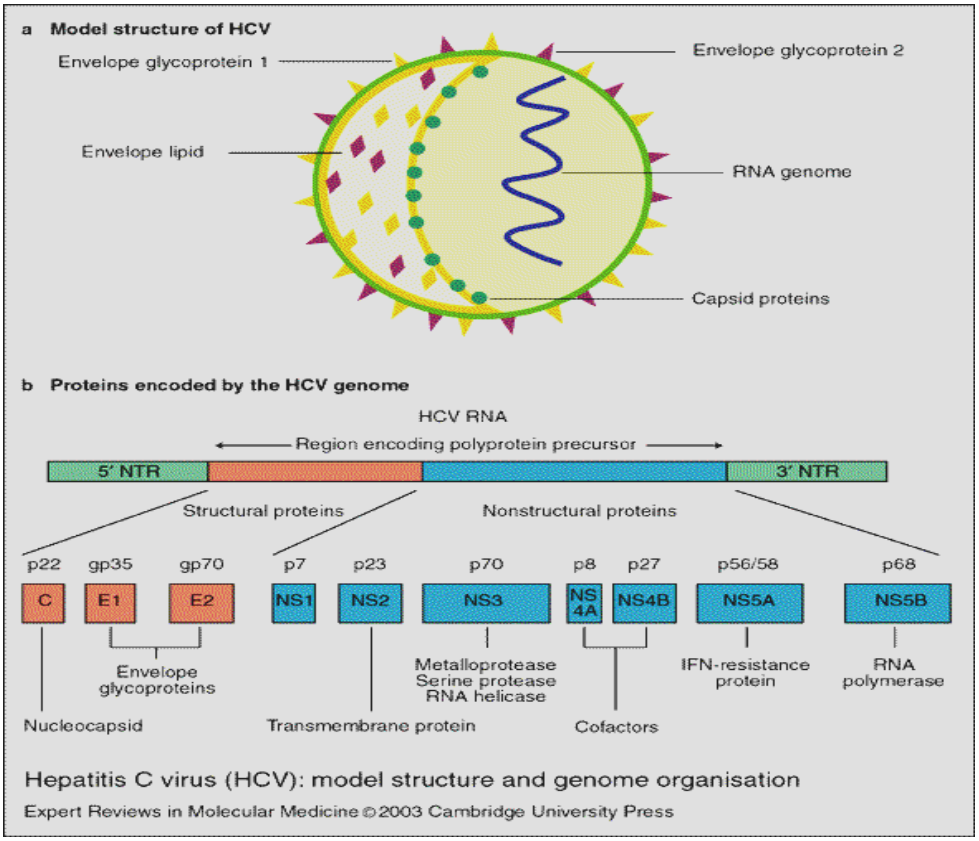

Figure (1): Structure of HCV **(Op De Beeck and Dubuisson, 2003).**

1.4.0. Mode of transmission

The primary route of transmission in the developed world is intravenous drug use (IDU), while in the developing world the main methods are blood transfusions and unsafe medical procedures. The cause of transmission remains unknown in 20% of cases. However, many of these are believed to be accounted for by IDU **(Maheshwari et al., 2010).**

1.5.0. Signs and symptoms

1.5.1. Acute infection:

Hepatitis C infection causes acute symptoms in 15% of cases. Symptoms are generally mild and vague including a decreased appetite, fatigue, nausea, muscle or joint pains, weight loss and rarely acute liver failure occur **(Wilkins et al., 2010).**

Symptoms typically last for 2 to 12 weeks, Alanine amino transferase (ALT) level may increase tenfold with HCV RNA determination by polymerase chain reaction (PCR) detectable often within days of acquisition. HCV antibody (anti-HCV) may not be measurable until after the development of clinical symptoms and occasionally is detectable only several weeks or months after individual has acquired acute HCV infection. Unlike hepatitis A and B viral infection, fulminant hepatic failure with acute HCV infection is rare **(Cheney et al., 2000).** Chronic infection develops in 85% of acutely affected individuals **(Bonkovsky and Mehta, 2001).**

1.5.2. Chronic infection:

About 85% of patients who are exposed to the virus develop a chronic infection. Most experience minimal or no symptoms during the initial few decades of the infection **(Arrieta et al., 2000)**.

Liver cirrhosis may lead to portal hypertension, ascites, easy bruising or bleeding, varices (enlarged veins, especially in the stomach and esophagus), jaundice, and a syndrome of cognitive impairment known as hepatic encephalopathy. It is a common cause for requiring a liver transplant **(Ozaras and Tahan, 2009).**

1.6.0. Diagnosis

There are a number of diagnostic tests for hepatitis C including: HCV antibody enzyme immunoassay or enzyme linked immunosorbent assay (ELISA), recombinant immunoblot assay and quantitative HCV RNA polymerase chain reaction (PCR).

1.6.1. Diagnostic Serological assay:

The enzyme linked immunosorbent assay (ELISA) is used to detect the presence of antibodies to the HCV. This test is rapid, sensitive and specific. If this test is positive, a confirmatory test is then performed to verify the immunoassay and to determine the viral load **(Wilkins et al., 2010).**

A positive ELISA indicates either past or recent HCV infection. It takes about 6–8 weeks following infection before the immunoassay will test positive. In low prevalence populations, the RIBA test remains useful in determining

whether an ELISA result is either a true or false positive **(Morishima and Gretch, 1999).**

Four generations of ELISA are currently available (ELISA-1, ELISA-2, ELISA-3, ELISA-4), each with increased sensitivity than its predecessor **(Godzik et al., 2012).** The incidence of false negative ELISA has been cut down to 2% with the fourth generation ELISA **(Rouet et al., 2015).**

1.6.2. Confirmatory assay:

RIBA is used to confirm diagnosis of HCV **(Ray et al., 2009).**

1.6.3. Detection of Viraemia.

Direct detection of virus using PCR can be done in patients infected with the virus and in immunosuppressed patients who may be antibodies negative. In addition, PCR is useful for determination of the status of patients with indeterminate antibody profiles. All patients presenting for treatment must be tested for viral load before starting treatment and PCR testing is necessary for monitoring the effect of treatment **(Wilkins et al., 2010).** There is a direct relationship between quantity of HCV viremia (HCV viral load) and severity of liver disease (**Ray et al., 2009).**

Although PCR is very sensitive, false-positive results are found probably resulting from contamination of the samples **(Gromb et al., 2000).**

1.6.4. Biopsy:

Liver biopsies are used to determine the degree of liver damage present.

1.7.0. Screening

It is believed only 5–50% of those infected in the United States become aware of their status.

Testing is recommended in those at high risk, which includes those with tattoos **(Jafari et al., 2010).**

1.8.0. Treatment

HCV induces chronic infection in 50–80% of infected persons. Approximately 40-80% of these clear with treatment **(Torresi et al., 2011).** In rare cases, infection can clear without treatment **(Ilyas et al., 2011).**

1.8.1. Interferon alpha INF:

INF alpha binds to specific receptors in the uninfected cells. This leads to the activation of various genes and the production of various enzymes that affect uncoating cell entry and increase natural killer (NK) cells **(Farrell et al., 1998).** Pegylated interferon-alpha-2a may be superior to pegylated interferon-alpha-2b, though the evidence is not strong **(Awad et al., 2010).** Improved outcomes are seen in 50–60% of people

(Wilkins et al., 2010). Duration of treatment varies according to viral genotype from 24 weeks to 48 weeks **(Foote et al., 2011).**

1.8.1.1. Side effect of INF therapy:

INF may lead to autoimmune disorders, such as hyperthyroidism or hypothyroidism and idiopathic thrombocytopenic purpura **(Cheney et al., 2000).**

1.8.1.2. Contraindication of INF therapy:

Contraindications for INF treatment are: pregnancy, depressive illness, leucopenia, alcohol drinking, hyperthyroidism, renal transplantation and autoimmune diseases **(Vakil and Caughan, 1998).**

1.8.2. Antiviral agents:

Antiviral drugs can play a role in the treatment of hepatitis C infection.

Sofosbuvir is a nucleotide analog used in combination with pegylated interferon and ribavirin, or with ribavirin alone for the treatment of hepatitis C virus (HCV) infection. Sofosbuvir inhibits the RNA polymerase that the hepatitis C virus uses to replicate its RNA **(Smith and Micheal, 2014).**

1.9.0. Prognosis

Responses to treatment vary by HCV genotype and is measured by sustained viral response. Sustained response is

about 40-50% in people with HCV genotype 1 given 48 weeks of treatment. Sustained response is seen in 70-80% of people with HCV genotypes 2 and 3 with 24 weeks of treatment **(Rosen, 2011).** Sustained response is about 65% in those with genotype 4 given 48 weeks of treatment. The evidence for treatment in genotype 6 disease is sparse **(Fung et al., 2008).**

2.0.0. HEPATITIS C VIRUS INFECTION AND SKIN DISEASES

2.1.0. Lichen planus

Lichen Planus (LP) is a chronic inflammatory mucoutaneous disease that was first described clinically by Wilson in 1869 and histologically by Dubreuilh in 1906, **(Mignogna et al., 2000).**

2.1.1. Pathogenesis

Lichen planus is a T cell mediated disease, an immune reaction against basal keratinocytes seems to be the major event in the development of LP **(Sugerman et al., 2002).** Upregulation of intercellular adhesion molecule-1 (ICAM-1) and cytokines associated with a Th1 immune response, such as interleukin (IL)-1 alpha,, and IL-8, may also play a role in the pathogenesis of lichen planus **(Chen et al., 2007 and Rhodus et al., 2007).**

2.1.2. Clinical picture

LP is characterized by pruritic, shiny, flat, purple papules and plaques. The papules retain the skin lines and are described as polygonal. The size of the papule is often fairly uniform in each patient. On the surface, there may often be seen a

reticulated pattern of white scale, known as Wickham's striae. The overall color is also often characteristic, and is described as violaceous. Papules may remain discrete or appear in-groups, in lines or in circles **(Katta, 2000).**

2.1.3. Prevalence

The prevalence of oral, cutaneous, pharyngeal, and/or vulval LP in 87 HCV-infected patients was 19.5% **(Nagao et al., 2008).** A retrospective analysis of 808 Italian patients with oral lichen planus showed that 17% of them were infected with HCV **(Carbon et al., 2009).** HCV is found more frequently in patients with generalized lichen planus, mucosal lichen planus, particularly the erosive variant or LP of chronic duration **(Jackson, 2002).**

The association of LP and positive serology for HCV as well as for positive RNA is not a substantive enough reason to determine the role of HCV in the pathogenesis of LP **(Arrieta et al., 2000)**.

2.2.0. Mixed cryoglobulinemia

Mixed cryoglobulinemia (MC) is a systemic vasculitis that affects mainly the small and, less frequently, medium-sized vessels and is attributable to the expansion of B cells producing pathogenic immunoglobulin M (IgM) with rheumatoid factor (RF) activity.