Hepatitis C virus and Hepatic Steatosis

Essay

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Hazem Talaat Abd El-Motelb

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List of Abbreviations

Alcoholic liver diseases	:	ALD
Alnine aminotransferase enzyme	:	ALT
Aspartate aminotransferase enzyme	:	AST
Adensne tri-phosphate	:	ATP
Branched dihydroxy nucleic acid test	:	b-DNA
Body mass index	:	BMI
Confidence interval	:	CI
Computerized tomography	:	CT
Diabetes mellitus	:	DM
Dihydroxy nucleic acid	:	DNA
Enzyme immunoassay test	:	EIA
Recombinant immunoassay test	:	EIBA
Enzyme linked immuno assay test	:	ELISA
Exposure prone procedures	:	EPPS
Fialouridine drug	:	FIAN
Gamma glutamyl transferase	:	GGT
Tlepstitis B surface antigen	:	HbsAg
Hepatitis B virus	:	HBV
Hepatitis B virus dihydroxy nucleic acid		HBVDNA:
Hepatitis C virus	:	HCV
Hepatitis C Virus	:	HCV
Hepatitis C virus ribonucliec acid		HCVRNA:
Health care wokers	:	HCWS
High density lipoproteins	:	HDL
Human immuno defiency virus	:	HIV

House field unit : HU

List of Abbreviations (Cont.)

Inflammatory bowel diseases	:	IBD
Intravenous drug users	:	IDU
Interferon	:	IFN
Immuno globulin G	:	IgG
Low density lipoproteins	:	LDL
Ministry of health program	:	MOHP
Magnetic resonance image	:	MRI
Non alcoholic fatty liver diseases	:	NAFLD
Non alcoholic steato hepatitis	:	NASH
Non coding regions	:	NCR
National health and nutritions examination survey		NHANES:
Non structural genes	:	NSG
Non structural proteins	:	NSP
Orthotopic liver transplantation	:	OLT
Odd's ratio	:	OR
Polymerase chain reaction test	:	PCR
Riboxynucleic acid	:	RNA
Serum glutamate oxaloacetic transaminase	:	SCOT
Structural genes	:	SG
Serum glutamate pyruvate transaminase	:	SGPT
Sustained viral response	:	SVR
Transcription mediated amplification test	:	TMA
Total parentral nutrition	:	TPN

Unites Kingdom	:	UK
United States of America	:	USA
World health organization	:	WHO

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الملخص العربي

إن الالتهاب الكبدي الوبائي الفيروسي (ج) يعتبر من أهم المشاكل التي تواجه المجتمع فى جميع أنحاء العالم، حيث يقدر عدد المصابين بالفيروس طبقاً لإحصائية منظمة الصحة العالمية (1999) بحوالي 170-200مليون شخص حول العالم.

ويعتبر الالتهاب الكبدي الوبائي فيروس (ج) مم أهم المشاكل التي تواجه المجتمع فى مصر حيث يقدر عدد الأشخاص الإيجابية للأجسام المضادة للفيروس فى مصر طبقاً لإحصائية وزارة الصحة المصرية بحوالي 7.2 مليون شخص مصري.

وأثناء إجراءات تشخيص الالتهاب الكبدي الوبائي الفيروسي (ج) عن طريق عينة الخلايا الكبدية ثبت وجود ترسب للدهون فى خلايا الكبد فى حوالي من 30-70% من عينات الخلايا مما يستوجب معه دراسة تأثير وجود الكبد الدهني على نشاط الفيروس فى خلايا الكبد.

والهدف من هذه الدراسة هو دراسة تفصيلية لتأثير ترسب الدهون فى خلايا الكبد على نشاط الفيروس وعلى تأثيره على خلايا الكبد وإحداث الضرر بها وكذلك دراسة أسباب هذه الترسبات وهل هي نتيجة تأثير الفيروس نفسه أم هي نتيجة وجود عوامل أخرى فى الشخص المصاب بالفيروس مثل وجود مرض السكر أو السمنة أو ارتفاع نسبة الدهون فى الدم.

إن دراسة تأثير وجود ترسبات دهنية بخلايا الكبد فى الأشخاص المصابين بالالتهاب الكبدي الفيروسي (ج) من الأهمية بحيث يؤثر فى

عملية تحديد نوعية العلاج للفيروس سواء كان بعقار الانترفيرون أو فى حالة إجراء عملية زراعة الكبد من حيث تأثير وجود الكبدي الدهني على احتمالية إعادة الالتهاب بعد عملية الزرع وكذلك نهدف من هذه الدراسة على دراسة تأثير خفض نسبة الدهون فى خلايا الكبد على تأثير الفيروس على تلك الخلايا وذلك عن طريق معالجة الأسباب التي تؤدي إلى ترسب الدهون فى تلك الخلايا مثل السكر والسمنة وارتفاع نسبة الدهون فى الدم.

وفي النهاية إن دراسة تأثير وجود ترسبات دهنية فى خلايا الكبد فى الأشخاص المصابين فيرس (ج) من الأهمية بمكان والتي تستدعي مواصلة البحث فى هذا المجال بما يفيد فى إمكانية تحديد تأثير ذلك الترسب على الفيروس نفسه وطريقة التعامل معه فى الأشخاص المصابين به.

Steatosis in Patients with Chronic HCV Infection

The mechanism by which HCV causes chronic, progressive liver damage are not exactly known. The lack of correlation between intrahepatic HCV RNA level and necroinflammation in chronic hepatitis C suggests that the HCV-associated liver damage is mostly immunomediated ***(Negro et al., 1999).***

Nonetheless, some histopathologic features,such as liver steatosis, are suggestive of a cytopathic effect of the virus ***(Goodman et al., 1995).***

Even when the most common causes of steatosis are excluded, fatty metamorphosis is present in about 30% of chronic HCV patients, a finding that is diagnostically relevant. The association between HCV genotype 3 and steatosis was reported firstly in 1997 by ***Mihm et al., (1997).*** This association raised the possibility of a direct effect of specific viral sequences on the pathogenesis of lipid accumulation ***(Mihm et al., 1997).***

Previous work has elucited some aspects of the relationship between HCV and steatosis; HCV-infected patients with steatosis are more likely to have risk factors for disease progression ***(Czaja et al., 1998).*** This association was subsequently confirmed by several studies ***(Adinolfi et al., 2001 and Serfaty et al., 2001).***

The role of liver biopsy in diagnosis of steatosis and chronic HCV:

Liver biopsy remains the best diagnostic tool for confirming nonalcoholic steatosis, as well as, the most sensitive and specific means of providing important prognostic information ***(Angulo et al.,1999).***

Although ultrasonography, computed tomographic scan, and magnetic resonance imaging can demonstrate hepatic fat accumulation, they can not grade the amount of steatosis or the associated necroinflammation or fibrosis ***(Clark et al., 2002 and Sanyal et al., 2002).***

Also, liver biopsy plays a central role in the evaluation of chronic liver diseases, including HCV infection of the liver ***(NIH, 1997).***

From 1997, a National Institute of Health (NIH) Consensus Development conference panel suggested that liver biopsy must be done prior to the beginning of treatment of HCV infection ***(NIH,1997).***

Liver biopsy provides a unique source of information on fibrosis and assessment of histology and the presence of steatosis in HCV patients ***(Walsh et al., 2004)***.

Liver biopsy is also useful to determine the effect of medical treatment, given the poor correlation between histological damage and the results of liver function tests or imaging studies ***(Angulo et al.,1999).***

Mechanism of Development of Hepatic Fibrosis in Patients with HCV Infection and Steatosis:

Steatosis of any cause can be associated with the development of inflammatory changes and fibrosis of

hepatocytes in the setting of oxidative stress ***(Day and James 1998).***

Sources of oxidative stress include mitochondrial dysfunction induced by drugs or viruses and an increase in intrahepatic iron concentration. These factors may result in the formation of reactive oxygen species, which may initiate lipid peroxidation which is associated with stellate cell activation and synthesis of collagen type 1,which is the major collagen in hepatic fibrosis ***(Lee et al., 1995).***

Hourigan et al. (1999) hypothesized that in HCV infection and steatosis, there is an increase lipid peroxidation, which in turn increases stellate cell activation and collagen synthesis which cause fibrosis.

Thus, chronic hepatitis C patients with a high grade of steatosis may represent a group at risk for more rapid progression to cirrhosis. In addition, a greater degree of periportal necrosis is observed in patients with higher steatosis and fibrosis scores. So steatosis, by promoting greater hepatic necrosis, may lead to fibrosis ***(Czaja et al., 1998).***

Czaja et al.. (1998) found higher amounts of IgG and more frequent autoantibodies in patients without steatosis, and suggested that the presence or absence of steatosis may reflect different pathogenic pathways, in which the presence of steatosis produce cytopathic-predominant processes while absence of steatosis may reflect immune-predominant processes ***(Czaja et al., 1998)***.

It has been suggested that steatosis acts by stimulating the free radical production associated with expression of the

HCV core protein, amplifying the cytopathic effect of HCV ***(Negro, 2002).***

Patients with liver steatosis and chronic HCV do not exhibit the classical features of steatohepatitis with ballooning degeneration or Mallory hyaline. However, many of the patients have zone 3 perisinusoidal fibrosis with a chicken-wire appearance, similar to that seen in steatohepatitis . The fatty liver appears to be more vulnerable to cellular injury from reactive oxygen species and inflammatory cytokines due to disturbance in hepatic energy hemostasis. The addition of new insults on a background of increased oxidative stress may result in marked ATP depletion and further hepatocyte necrosis. These findings may help to explain the increased susceptibility of a steatotic liver to other forms of liver injury which occurs in viral hepatitis ***(Day and James, 1998).***

So, in chronic HCV infection, steatosis is an important cofactor in accelerating the development of hepatic fibrosis and in increasing necroinflammatory activity of hepatocytes ***(Hourigan et al., 1999).***

In addition to a role of steatosis in accelerating of hepatic fibrosis in chronic HCV patients, steatosis may adversely affect the response of hepatocytes to antiviral therapy ***(Poynard et al., 2003).***

Prevalence of steatosis in HCV patients:

Steatosis is seen in 30-70 % of liver biopsies from patients with chronic hepatitis C ***(Adinolfi et al., 2001)*** more frequently than is seen in other causes of chronic hepatitis ***(Rubbia-Brandt et al., 2001)***. In a high proportion of these