Atherosclerosis as a Possible Extrahepatic Manifestation of Chronic Hepatitis C Virus Infection in Egyptian Patients

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Abstract

There are 170 million people affected with chronic hepatitis C virus (HCV) infection worldwide. Egypt has the highest HCV prevalence in the world (overall prevalence of HCV antibody is 12% among the general population and reaches 40% in persons 40 years of age and above in rural areas. Our study aimed to study the correlation between hepatitis C and carotid atherosclerosis in Egyptian patients via assessing the intima medial thickness and carotid plaques.

Patients and Methods: We evaluated one hundred patients, fifty (50) patients with seropositive HCV and fifty (50) HCV negative patients by full clinical history, physical examination, laboratory assessment including RT-PCR for All HCV positive patients and Color flow Doppler study of both common carotid arteries to assess The carotid intima medial thickness A thickness more than 1mm was considered significant while a thickness more than 1.3mm will be diagnosed as a plaque.

Results: In our study there was significant statistical difference between case and control as regarding the common carotid artery intima media thickness (0.93 ± 0.4 vs. 0.67 ± 0.10; p < 0.001) and a positive association between chronic HCV infection and CIMT: Eleven patients of HCV seropositive have increased CIMT (1mm or more (22%) And two patients have carotid plaque CIMT more than 2mm (4%).

Conclusion: Our work provided a positive correlation between the chronic HCV infection and CIMT as an indicator of atherosclerosis which makes screening for asymptomatic atherosclerosis of great importance.

Key Words: HCV – Carotid intema medial thickness – Plaque.

Introduction

THERE are 170 million people affected with chronic hepatitis C virus (HCV) infection, which may cause liver cirrhosis and hepatocellular carcinoma, worldwide [1].

In Egypt, schistosomiasis was traditionally the most important public health problem and infection with Schistosoma mansoni was the major cause of liver disease. From the 1950s until the 1980s, The Egyptian Ministry of Health (MOH) undertook large control campaigns using intravenous tartar emetic, the standard treatment for schistosomiasis, as community-wide therapy. This commendable effort to control a major health problem unfortunately established a very large reservoir of hepatitis C virus (HCV) in the country [2].

It was evident when diagnostic serology became available in the1990s that HCV had replaced schistosomiasis as the predominant cause of chronic liver disease [3]. In addition, the prevalence of hypertension is 8.9% of adult Egyptians and the overall prevalence of central obesity among Egyptian adults, according to the 2 indicators waist circumference (WC) and waist to hip (WHR) ratio are 24.1% and 28.7% respectively [4].

Cerebrovascular disease is the second leading cause of death worldwide and the leading cause of acquired disability in adults in most regions [5].

Several infectious agents have been associated with atherosclerosis. HCV infection manifests some peculiar characteristics which support its possible role in atherosclerosis. It has been associated with systemic vasculitides [6], increased concentration of soluble intercellular adhesion molecules [7] and the presence of anti-endothelial antibodies [8].

Carotid intema media thickness is a powerful predictor of coronary and cerebrovascular events [9,10]. Specifically, carotid IMT exceeding 1mm has been associated with three to four times the risk of subsequent ischemic stroke [11].

An international multicentre population-based study has identified cardiac diseases, hypertension,
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diabetes, smoking, alcohol intake, unhealthy diet, and abdominal obesity, lack of exercise, psychosocial stress and depression as risk factors associated with 90% of stroke risk [12].

These risk factors cannot completely explain the occurrence of the disease, new risk factors including infectious agents have been documented [13,14]. Altered cerebral metabolism in patients with chronic HCV infection has been proposed [15].

Earlier studies showed that HCV seropositivity was independently associated with atherosclerosis [13,16]. However, subsequent research yielded conflicting results; some confirming [17,18] and others deny such an association [19,20]. Moreover, the effect of viral load, genotype and severity of cirrhosis in chronic HCV infected patients is unknown.

Chronic HCV Infection is considered an independent risk predictor of cerebrovascular mortality, whether HCV infection increases the incidence of stroke are undetermined [21]. Several mechanisms of this effect have been suggested; low-density lipoprotein receptor may promote HCV endocytosis [22,23] and oxidative stress induced by HCV core protein can potentiate the oxidation of lipoprotein in atherosclerotic plaques [24]. In addition, Oliveira, et al., (2007) reported that activation of TNF- a system and high IL-6 levels could contribute to increased insulin resistance and higher cardiovascular risk [25].

Patients and Methods

After an educated consent, One hundred (100) patients were included; fifty (50) patients with seropositive HCV and fifty (50) HCV negative patients were browsed from the words and outpatients of Kasr El-Ainy Hospital. We started at December 2010 and finished at October 2012.

Inclusion criteria:
Both sexes aged from 18-60 years old.

Exclusion criteria:
• Diabetes mellitus.
• Hypertension.
• Myocardial infarction or PTCA in the past three months.
• Suspected cancer.
• Carotid surgery.
• Known chronic inflammatory condition.
• Chronic kidney disease.

All candidates will be subjected to: Full clinical history and physical examination including age, sex, BMI, history of hypertension, diabetes mellitus, smoking as well as family history of premature coronary events, and hepatitis C treatment. Laboratory assessment including: HCV antibodies, liver enzymes, fasting and 2 hours postprandial blood glucose, full lipid profile, CRP, and creatine kinase. Where all HCV positive patients were assessed for viral load via RT-PCR. Color flow Doppler study of both common carotid arteries to assess presence or absence of carotid plaques. The carotid intima medial thickness will be assessed by M mode image. The mean of three consecutive readings will be taken. A thickness more than 1mm was considered significant according to PREVEND IT study [31].

The definition of plaque was more than 1.3mm in some studies [16] and more than 2.0mm in other studies [17]. The number and severity of plaques in the internal carotid artery were assessed and evaluated.

The Doppler study was done at the vascular laboratory of the internal medicine department of Kasr El-Ainy Hospital, Cairo University.

Statistical analysis:
Analysis of data was done by IBM computer using SPSS (statistical program for social science version 12).

Description of quantitative variables as mean, SD and range [26].
• Description of qualitative variables as number and percentage.
• Chi-square test was used to compare qualitative variables between groups.
• Unpaired t-test was used to compare quantitative variables, in parametric data (SD <50% mean).
• Mann Whitney test was used instead of t-test in non parametric data SD >50% mean.
• Spearman Correlation co-efficient test was used to rank variables versus each other positively or inversely p-value >0.05 insignificant.

p<0.05 significant and p<0.01 highly significant.

Results

The study was done for one hundred patients distributed on two equal groups, fifty cases HCV positive patients and fifty HVC negative controls
Table (1) shows no statistically significant differences between both groups as regard the risk factors.

Table (2) shows statistically significant differences between both groups as regard bilirubin, platelets, albumin and liver enzymes data by using unpaired \( t \)-test. On the other hand there is no significant difference as regard other variables.

Regarding general data only age of the patient was significantly related to carotid intima medial thickness among both cases and controls as shown in Tables (3,4) and Figs. (1,2).

Both Table (5) and Fig. (3) show that cases had a higher IMT on both sides and totally with statistically significant difference between both groups by using unpaired \( t \)-test.

Table (1): Comparison between both groups as regard the risk factors.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls N=50</th>
<th>Cases N=50</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>116.1±29.9</td>
<td>112.2±28</td>
<td>&gt;0.05 NS</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>73.8±7</td>
<td>73.2±6</td>
<td>&gt;0.05 NS</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>93.5±11</td>
<td>92±14</td>
<td>&gt;0.05 NS</td>
</tr>
<tr>
<td>2 hours post prandial</td>
<td>125±14</td>
<td>124±12</td>
<td>&gt;0.05 NS</td>
</tr>
<tr>
<td>blood glucose</td>
<td>5.4±0.9</td>
<td>5.5±0.9</td>
<td>&gt;0.05 NS</td>
</tr>
<tr>
<td>Glycated hemoglobin</td>
<td>159±24</td>
<td>151±28</td>
<td>&gt;0.05 NS</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>42.1±5.5</td>
<td>43.5±10</td>
<td>&gt;0.05 NS</td>
</tr>
<tr>
<td>High density lipoprotein</td>
<td>83.2±10</td>
<td>82±11</td>
<td>&gt;0.05 NS</td>
</tr>
<tr>
<td>Low density lipoprotein</td>
<td>125±30</td>
<td>115±40</td>
<td>&gt;0.05 NS</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>125±30</td>
<td>115±40</td>
<td>&gt;0.05 NS</td>
</tr>
</tbody>
</table>

Table (2): Comparison between both groups as regard laboratory data.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls N=50</th>
<th>Cases N=50</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin</td>
<td>0.95±0.2</td>
<td>2±0.8</td>
<td>&lt;0.001 HS</td>
</tr>
<tr>
<td>Albumin</td>
<td>4.2±0.4</td>
<td>3.4±1</td>
<td>&lt;0.001 HS</td>
</tr>
<tr>
<td>AST</td>
<td>33.2±39</td>
<td>53.8±30</td>
<td>&lt;0.001 HS</td>
</tr>
<tr>
<td>ALT</td>
<td>32±10</td>
<td>50±20</td>
<td>&lt;0.05 NS</td>
</tr>
<tr>
<td>GGT</td>
<td>32.2±6</td>
<td>40.8±9</td>
<td>&lt;0.001 HS</td>
</tr>
<tr>
<td>PC</td>
<td>6±0.2</td>
<td>0.7±0.2</td>
<td>&gt;0.05 NS</td>
</tr>
<tr>
<td>Platelets</td>
<td>309±79</td>
<td>190±80</td>
<td>&lt;0.001 HS</td>
</tr>
<tr>
<td>CK</td>
<td>91.6±13</td>
<td>93.2±15</td>
<td>&gt;0.05 NS</td>
</tr>
<tr>
<td>CRP</td>
<td>6.2±1.5</td>
<td>6.6±1.4</td>
<td>&gt;0.05 NS</td>
</tr>
</tbody>
</table>

Table (3): Correlation between intima media thickness versus general data among controls.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Right IMT</th>
<th>( r )</th>
<th>( p )</th>
<th>Left IMT</th>
<th>( r )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.43</td>
<td>&lt;0.001 HS</td>
<td></td>
<td>0.09</td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.18</td>
<td>&gt;0.05</td>
<td></td>
<td>0.12</td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>0.08</td>
<td>&gt;0.05</td>
<td></td>
<td>0.17</td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>0.12</td>
<td>&gt;0.05</td>
<td></td>
<td>0.13</td>
<td>&gt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

Table (4): Correlation between carotid intima media thickness and general data among cases.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Right IMT</th>
<th>( r )</th>
<th>( p )</th>
<th>Left IMT</th>
<th>( r )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.48</td>
<td>&lt;0.001 HS</td>
<td></td>
<td>0.35</td>
<td>&lt;0.05S</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>0.11</td>
<td>&gt;0.05</td>
<td></td>
<td>0.19</td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>0.09</td>
<td>&gt;0.05</td>
<td></td>
<td>0.03</td>
<td>&gt;0.05</td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>0.16</td>
<td>&gt;0.05</td>
<td></td>
<td>0.13</td>
<td>&gt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

Table (5): Comparison between both groups as regard intima media thickness.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Controls N=50</th>
<th>Cases N=50</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right IMT</td>
<td>0.67±0.10</td>
<td>0.93±0.4</td>
<td>&lt;0.001 HS</td>
</tr>
<tr>
<td>Left IMT</td>
<td>0.69±0.2</td>
<td>0.93±0.3</td>
<td>&lt;0.001 HS</td>
</tr>
<tr>
<td>Average IMT</td>
<td>1.02±0.1</td>
<td>1.39±0.6</td>
<td>&lt;0.001 HS</td>
</tr>
</tbody>
</table>

Discussion

Chronic HCV Infection is considered an independent risk predictor of cerebrovascular mortality [21]. Several mechanisms of this effect have been suggested; low-density lipoprotein receptor may promote HCV endocytosis [22,23] and oxidative...
stress induced by HCV core protein can potentiate the oxidation of lipoprotein in atherosclerotic plaques [24]. In addition, Oliveira, et al., (2007) reported that activation of TNF-α system and high IL-6 levels could contribute to increased insulin resistance and higher cardiovascular risk [25].

In the present study both HCV patients and HCV negative control had similar atherosclerotic risk profile, as there was no statistically significant difference between their ages and lipid profile in addition diabetic patients had been excluded.

In our study there was significantly statistical difference between both HCV patients and HCV negative control as regarding the common carotid artery intima media thickness (0.93 ± 0.4 vs 0.67 ± 0.10; p < 0.001). This suggested the direct effect of HCV on IMT and coincided with what was reported by Boddi, et al., (2010) who found RNA sequences of HCV inside carotid plaques and showed that HCV replicates within carotid atheroma, supporting the hypothesis of a direct pro-atherogenic role of HCV [27].

In the present study we have found a positive association between chronic HCV infection and CIMT: Eleven HCV seropositive patients have significant high CIMT (1mm or more (22%).

The definition of plaque was more than 1.3mm in some studies 16 and more than 2.0mm in other studies [17].

In the present study the plaque definition was >1.3mm thickness. By this definition five of our HCV patients have carotid plaque CIMT more than 1.3mm (10%). And two patients have CIMT more than 2mm (4%).

In a similar study Petta et al., (2010) evaluated the prevalence of carotid atherosclerosis in 174 biopsy proven chronic hepatitis C patients compared with 174 control and found CIMT was higher in chronic hepatitis C patients (1.04 ± 0.21 vs 0.96 ± 0.16; p < 0.001) and carotid plaques (defined as focal thickening > 1.3) are found in 73 patients (41.9%) compared to 40 (22.9%) in control group; (p < 0.001) [28]. This goes with what was reported by Kiechl et al. (2001) in a prospective population-based survey on the pathogenesis of atherosclerosis. In 826 men and women 40 to 79 years old (1990 baseline), 5-year changes in carotid atherosclerosis were thoroughly assessed by high-resolution duplex scanning found that Chronic infections amplified the risk of atherosclerosis development in the carotid arteries. The association was most pronounced in subjects free of carotid atherosclerosis at baseline for any chronic infection [29].

Our study provides that age was found to have a significant positive correlation with CCIMT among controls and cases.

Tomoko Ishizu et al., (2004) found that Mean IMT increased in a linear manner with age. This correlation remained significant after adjustment for gender, smoking, systolic and diastolic blood pressure, body mass index, and serum concentrations of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides [30].

References


Atherosclerosis as a Possible Extrahepatic Manifestation

The abstract and the aims of the study: There are 10 million patients suffering from hepatitis C worldwide, and 12% of them are HCV patients. In the world, the prevalence of hepatitis C is 40% among people over 40 years old. This study aimed to investigate the relationship between hepatitis C and the occurrence of atherosclerosis in the abdominal arteries and the characteristics of the plaques. The study was conducted on 100 patients diagnosed with hepatitis C and 100 healthy controls. The diagnosis was confirmed by RT-PCR for the HCV viral RNA. The plaques were evaluated using grayscale imaging. The results showed a significant correlation between hepatitis C and atherosclerosis in the abdominal arteries. The study also found that the plaques were larger and more complex in the hepatitis C group compared to the control group. The conclusion of the study is that hepatitis C is a possible extrahepatic manifestation of atherosclerosis.