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Abstract

Background: Coronary artery disease (CAD) is one of the leading causes of death worldwide. Predisposing factors include some infectious aetiologies that have a systemic effect like hepatitis C virus.

Aims: The aim of this study was to explore the association between hepatitis C viral infection and coronary artery disease.

Methods: This case–control study was designed to include 100 patients attending the Cardiology Department in Tanta University Hospital, Gharbia Governorate, Egypt, for diagnostic angiography. A consecutive sample of 50 patients with abnormal angiographic findings was matched with another 50 consecutive patients with normal angiographic findings regarding age, sex, and major risk factors for coronary artery disease (diabetes mellitus, hypertension and smoking). Patients were investigated for hepatitis C virus (HCV) infection.

Results: We found that 46% of abnormal angiography were HCV-positive compared to 28% of patients with normal angiography; this difference was not statistically significant. On studying the number of vessels affected among patients with abnormal angiography it was noted that one vessel affection was found mainly among HCV-negative patients (59.3% compared to 17.4% among HCV-negative and -positive patients). Multi-vessel affection was found mainly among HCV-positive patient (47.8% compared to 22.2% among HCV-positive and -negative respectively).

Conclusions: The possible association between HCV positivity and extension of coronary artery disease may refer to the role of HCV in coronary artery disease pathology. Further studies on a large scale to investigate this association are recommended.

Keywords: coronary disease, stenosis, atherosclerosis, hepatitis C

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Introduction

Ischaemic heart disease, became one of the major killers worldwide during 2012 (1). Recently, it has become the leading cause of death in Egypt and has started to affect younger age groups (2).

Many epidemiological studies found an association between several infectious etiologies and coronary artery disease (CAD) mainly due to alterations in blood lipids (3–5). The inflammation hypothesis of atherosclerosis postulates that the key events involved in the initiation and progression of the lesion are represented mainly by inflammatory and fibro-proliferative processes triggered by cytokines and growth factors. However, one of the most interesting recent developments has been the idea that infective agents may provoke a pro-inflammatory effect and have a significant role in atherothrombosis (6).

In the early 1970s, the monoclonal hypothesis was first proposed. This suggested a potential

role for viral infection in the atherosclerotic process. Specifically, this theory proposed that a mutation or a viral agent may represent events able to transform a single smooth muscle cell into the progenitor of a proliferative clone (7).

Hepatitis C virus (HCV) causes chronic liver disease and adds to the disease burden globally, The World Health Organization has declared HCV a global health problem, with approximately 3% of the world's population (roughly 170–200 million people) infected with HCV. In the United States of America, approximately 3 million people are chronically infected (4). Egypt has the highest prevalence of HCV in the world, with a national prevalence of 10–13% (8,9).

Generally, HCV causes hepatic manifestations but extra-hepatic manifestations have also been documented (10). Common extra-hepatic manifestations include thyroid disorder and type II Diabetes Mellitus. Some studies have found an association between HCV infection and dilated cardiomyopathy and myocarditis (11,12) and alterations in lipid metabolism (3,5,6). This association with alteration in the lipid metabolism has led some researchers to suspect HCV infection as a risk factor for CAD, with some studies reporting an increased risk or an increase in measures of subclinical atherosclerosis (13–16).

Scanty data on the relationship between HCV infection and atherosclerosis are available with some studies showing an association between HCV seropositivity and carotid artery plaque and carotid intima–media thickening, independent from other risk factors for atherosclerosis (13,17). The present study was undertaken to study the relationship or association of active viral replication [polymerase chain reaction (PCR) positive] with number of cardiac vessels blocked.

Methods

Study design

This was a case–control study in which the presence of HCV infection was compared in patients having known CAD with controls who did not have CAD; without adjusting for CAD risk factors.

Study setting

The study was carried out in the Cardiology Department, Tanta University Hospital, a teaching hospital in Tanta City, Gharbia Governorate in the middle of the Nile Delta, northern Egypt. The hospital also serves the surrounding governorates. The cardiology department has 40 beds. Data were collected from 1 June 2011 to end of December 2011 from patients attending the cardiology department for diagnostic catheterization (coronary angiography)

Sampling

We selected 50 consecutive patients with abnormal findings in coronary angiography sufficient to diagnose CAD (defined as > 50% stenosis of one of the proximal coronary arteries). These were matched for age, sex and major risk factors (diabetes mellitus, hypertension and smoking status). Another 50 consecutive patients with normal coronary angiography were also tested for viral markers and they served as controls.

Patients having ≥ 1 of the following conditions were not included in the study: those having other viral hepatitis, especially hepatitis B; those with impaired liver or kidney function; and those with uncontrolled diabetes, acute or chronic inflammatory disease or history/presence of neoplastic disease. At our centre, all patients undergoing coronary angiography undergo full medical history taking and general and local clinical examination, 12-leads surface ECG, echocardiography and routine laboratory investigations, including prothrombin time, partial thromboplastin time, kidney function test, liver function test and random blood sugar test.

Testing for HBsAg and anti-HCV was also done using the ELISA (enzyme-linked immunosorbent assay) technique to exclude these infections. Positive cases were tested further using the qualitative PCR technique to confirm the viral replication. Coronary angiography was done using the femoral approach (18) and standard imaging technique (19).

Ethical considerations

The protocol of the study was approved by the ethical committee of Tanta University Faculty of Medicine and verbal consent was taken from patients while maintaining patient confidentiality.

Statistical analysis

Data were analysed using SPSS, version 11. The chi-squared test was used for a qualitative data and student t-test for quantitative data. Results were considered statistically significant at the 5% level.

Results

A total of 100 patients were included in this study, 57 males and 43 females (Table 1). There was no significant difference between cases, i.e. those having abnormal angiography, and controls, i.e. those with normal angiography, in regard to age, sex and residence.

Overall 27% of the study participants had diabetes mellitus, 57% had hypertension and 34% were smokers (Table 2). There was no significant difference between cases (abnormal angiography) and controls (normal angiography) regarding these risk factors for CAD. Although 46% of the patients who had CAD were HCV-positive compared with only 28% of those who had no CAD, the difference was not statistically significant (P = 0.062) (Table 3).

In 47.8% of the HCV-positive patients, more than 2 vessels were affected compared with 22.2% of the HCV-negative patients. Among the HCV-negative patients, 59.3% showed affection of one vessel only compared with 17.4% who were HCV-positive and this difference was statistically significant (P = 0.0105) (Table 4). Patients who were HCV-seropositive had more vessels affected than those who were HCV-seronegative.

Discussion

Our study showed that patients with multiple vessel coronary artery disease were more likely to suffer from concomitant active hepatitis C infection than those who had single vessel disease. Several studies have investigated the extra-hepatic manifestation of HCV, but there has been little research investigating the relationship between HCV and cardiovascular disease (18). The association between HCV infection and CAD is less clear. A small number of studies have shown conflicting results; some have reported no association between HCV infection and CAD (19–21), while other research has reported an increased risk or an increase in measures of subclinical atherosclerosis (17).

Tsui et al. analysed data from a cohort of patients with stable coronary heart disease and found that HCV-seropositive patients had higher rates of death, cardiovascular events and hospitalization because of heart failure during the follow-up despite lower cholesterol and C-reactive protein levels (22). After adjustment for age and cardiovascular risk factors together with the inflammatory markers level the cardiovascular events remained 50% greater in the HCV-positive group, but the difference was not significant. Despite having a greater number of patients (981) in their study, they were broader in regard to CAD diagnosis as they included all patients with a history of myocardial infarction, coronary angiographic stenosis > 50%, and patients with positive treadmill test, which may introduce some inaccuracies. In contrast, our study included only patients diagnosed using the gold standard method, which is diagnostic coronary angiography showing > 50% stenosis.

Since HCV virus is endemic in Egypt, many researchers are also studying the association of heart disease primary risk factors that may be specific to our country. Egyptian researchers have studied the metabolic and cardiovascular risk profiles and hepatitis C virus infection in rural Egypt and found a positive relationship between HCV infection and some cardiovascular risk factors such as elevated triglycerides (23).

Okasha and Fayez studied 202 patients who were referred for coronary artery disease. All patients were investigated for HCV infection. The results of coronary angiography were compared between HCV-positive and negative patients and they found that HCV infection had no impact on development of CAD. Coronary angiographic findings are not different between HCV-positive and negative patients with more left descending coronary artery affection in positive cases (24).

Vassalle et al. investigated 491 patients with CAD and a control group of 195 patients and found that HCV seropositivity was 2.0% in control subjects and 6.3% in the CAD group; HCV seropositivity also increased with the number of vessels affected. Univariate logistic regression analysis showed that, in addition to other conventional atherogenic risk factors such as age, sex, smoking, hypertension, diabetes and dyslipidaemia, HCV seropositivity was associated with CAD (odds ratio 3.2). Multivariate logistic regression analysis showed that HCV seropositivity still represented an independent predictor for CAD (odds ratio 4.2; P

It has been reported that HCV infection accelerates atherosclerosis (23,25); this may be a result of the inflammatory process due to the infection itself; moreover, the prevalence of HCV increases with age and increasing age is also a risk factor for CAD. This may explain the increased number of vessels affected in HCV-positive patients as has been reported in our study.

Butt et al. reported that, despite having a better risk profile of being younger and with a better lipid profile, HCV-infected subjects were at a significantly higher risk of developing CAD compared with HCV-uninfected subjects, even after adjustment for other risk factors for cardiovascular disease (18). This is also concordant with our results that showed that HCV seropositivity was higher among patients with CAD compared with patients with normal coronary arteries; however, the difference was not statistically significant, possibly due to the limited number of our study population compared to the study of Butt et al.

In contrast, other studies (19–21) discount such a relationship, either in stable CAD patients or those with acute myocardial infarction (21,24). It is possible that the disparate findings might be due to differences in the populations examined, outcomes evaluated, and confounding variables

used in the multivariate analyses.

As HCV infection is endemic and highly prevalent in Egypt, a considerable proportion of patients with abnormal angiography were HCV-positive and a significant relationship was found between HCV infection and the number of vessels affected, this may call for other studies that include a larger number of cases and longer duration of follow-up to document the associations.

The current study had the following limitations: the results were from a single medical centre (Tanta University Hospital) and the sample size was small. Also, some risk factors, such as dyslipidaemia, were not matched while others, such as diabetes mellitus and hypertension, were not matched according to disease severity or control, which may affect the coronary arteries.

Nevertheless, from the results of this study the following actions may be considered: enforcement of preventive measures for HCV infection, especially among risk groups; screening of the apparently normal population for early detection and management of HCV infection to reduce its effect on coronary arteries; and routine HCV infection testing for every cardiac patient not only for those undergoing catheterization but also for those under medical treatment.

Funding: None.

Competing interests: None declared.

Association entre coronaropathie et séropositivité au virus de l’hépatite C

Résumé

Contexte : La coronaropathie constitue l’une des principales causes de mortalité dans le monde. Ses facteurs prédisposants comprennent certaines étiologies infectieuses ayant un

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effet systémique à l’instar du virus de l’hépatite C. .

Objectif : L’objectif de cette étude était d’examiner la possibilité d’une association entre l’infection par le virus de l’hépatite C et la coronaropathie.

Méthodes : La présente étude cas-témoins a été conçue pour inclure 100 patients venant en consultation au département de cardiologie du Centre hospitalier universitaire de Tanta, dans le gouvernorat de Gharbeya (Égypte), pour une angiographie à visée diagnostique. On a comparé un échantillon consécutif de 50 patients présentant des résultats angiographiques anormaux à un autre groupe de 50 patients consécutifs pour lesquels les résultats angiographiques étaient normaux en prenant en compte l’âge, le sexe et les principaux facteurs de risque de coronaropathie (diabète sucré, hypertension et tabagisme). Les patients ont été soumis à un test de dépistage de l’infection par le virus de l’hépatite C (VHC).

Résultats : 46 % des patients présentant des résultats angiographiques anormaux étaient positifs au VHC, contre 28 % chez ceux pour lesquels les résultats angiographiques étaient normaux ; cette différence n’était pas statistiquement significative. Après examen du nombre de vaisseaux concernés chez les patients dont les résultats angiographiques étaient anormaux, une seule atteinte vasculaire a été observée, principalement chez les patients négatifs au VHC (59,3 % parmi les patients négatifs au VHC contre 17,4 % chez les patients positifs au VHC). On a observé, principalement chez les patients positifs au VHC, que plusieurs vaisseaux étaient atteints (respectivement 47,8 % et 22,2 % parmi les patients positifs au VHC et négatifs au VHC).

Conclusion : Une association éventuelle entre la séropositivité au VHC et l’étendue de la coronaropathie pourrait être liée au rôle joué par le VHC dans la pathologie de cette maladie. Des recherches plus poussées et de grande ampleur sont recommandées afin d’étudier plus en détail cette association.

الارتباط بين مرض الشريان التاجي والإيجابية المصلية لفيروس التهاب الكبد **C**

أسامة شعيب، مدحت عشماوي، سهام بدر، محمود العمروسي

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