

Association Between Hepatitis C Virus Infection and Clinical Atherosclerosis at The University Hospital of Cotonou, Comparative Cross-Sectional Study in 105 Patients

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ABSTRACT

Introduction: Many studies have shown that chronic hepatitis C virus (HCV) infection is an additional and independent risk factor for coronary heart disease, carotid atherosclerosis and cerebrovascular accidents (stroke). The purpose of this work was to study the association between HCV infection and clinical atherosclerosis in a hospital in Cotonou.

Patients and Methods: This was a comparative cross-sectional study that took place from 02 to 30 November 2018 at the Department of Cardiology at the University Hospital of Cotonou. The cases followed were patients followed for clinical atherosclerosis and were compared to controls with no clinical history of atherosclerosis and followed for diagnosed hypertension (hypertension) less than 5 years old. Sociodemographic data and the prevalence of HCV infection were compared in the two groups. The diagnosis of hepatitis C virus (HCV) infection was performed by a Hepatitis C Virus Test Strip® rapid diagnostic orientation test, HCV confirmation serology by ELISA (Enzyme-linked immunosorbent assay) and the "Polymerase Chain Reaction" (PCR) for the determination of the HCV viral load. Data analysis was performed using EpiData version 3.1 and Epi Info software. A value of $p < 0.05$ was considered statistically significant.

Results: Among the 105 subjects included, there were 53 cases (50.3%) and 52 controls (49.5%). The mean age of the subjects was 59.7 years \pm 11.0 with no significant difference between cases and controls ($p=0.56$). Cases and controls were comparable across all conventional atheromatous risk factors outside of hypertension, which had a higher prevalence among controls ($p=0.002$). Acute coronary syndrome was the most common clinical form of atherosclerosis in 94.3% of cases. Of the 105 subjects in the study, the HCV rapid screening test was positive in 4 (3.8%), including 2 cases (3.8%) and 2 controls (3.8%). There was no significant association between HCV infection and the presence of clinical atherosclerosis ($p=0.68$). One of the two cases had an undetectable charge.

Conclusion: Chronic HCV infection would not be associated with clinical atherosclerosis in our study. A larger study, including a larger number of cases and controls, is needed to clarify these data.

Keywords

Hepatitis C, Clinical atherosclerosis, Association.

Introduction

Hepatitis C (HCV) is a public health problem with currently nearly

71 million chronic carriers worldwide [1]. The majority of people infected with this virus (85%) will develop a chronic infection [2]. This chronic infection will progress to cirrhosis in 10 to 20% in 20 years with an annual incidence of 1 to 4% of hepatocarcinoma in the cirrhosis stage [3,4]. Chronic forms of hepatitis C are most

often the cause of death due to their complications, cirrhosis and hepatocellular carcinoma. HCV can also lead to many extrahepatic manifestations; dermatological, neurological, hematological, rheumatological, renal and ophthalmic [5,6].

Also in recent years, particular attention has been paid to the effects of HCV on the cardiovascular system, and the relationship between chronic HCV infection and the risk of coronary heart disease and the occurrence of Cerebrovascular Accidents.

In particular, HCV-infected subjects have been reported to experience more cardiovascular events [7], with an increased incidence of acute myocardial infarction and unstable angina [8], as well as the development of atherosclerotic plaques [9]. In addition, many retrospective and prospective studies suggest that HCV-infected individuals may be at higher risk of stroke and stroke death [10,11].

However, the mechanisms leading to the increased risk of cardiovascular complications in HCV-infected subjects are not yet well understood [12], and there is no general consensus on such an association. As a result, several studies have recently challenged the above data [13,14], and some clinical evidence even suggests that HCV may have a protective effect against the atherosclerosis process [15].

The purpose of this work is to study the association between HCV infection and clinical atherosclerosis at the University Hospital of Cotonou in Cotonou.

Patients and Methods

This was a comparative cross-sectional study that took place from 02 to 30 November 2018 at the University Hospital of Cotonou in Cotonou. Patients hospitalized for clinical atherosclerosis between 2012 and 2017 and identified from hospitalization records were compared to controls without clinical atherosclerosis.

Clinical atherosclerosis was defined as acute coronary syndrome, non-cardioembolic ischemic stroke, carotid atheroma or obliterating arteriopathy of the lower limbs at any stage of development.

- Acute coronary syndrome was evidenced by an electrocardiogram (ECG) and/or troponin I assay.
- Ischemic stroke was retained on the existence of a focused sensory motor deficit with a CT scan confirming cerebral ischemia. The absence of cardio-embolic cause was evidenced by a cardiac ultrasound and 24-hour ECG using the Holter method, which did not reveal any supraventricular rhythm disorders such as flutter or atrial fibrillation.
- Carotid atheroma was confirmed by Döppler ultrasound of the supra-aortic trunks; obliterant arteriopathy of the lower limbs was retained on the existence of claudication of the lower limbs or on the confirmation of Döppler ultrasound of the lower limbs.

Controls were included consecutively during the study period

among patients admitted to outpatient cardiology for follow-up of high blood pressure diagnosed less than 5 years ago. They had no history of acute coronary events, stroke, transient ischemic attack or intermittent claudication of the lower limbs. They received a complete clinical examination and ECG to rule out any clinical manifestations of atherosclerosis.

Anthropometric data were collected and a history of classical atheromatous risk factors (hypertension, diabetes, dyslipidemia, smoking) was collected from medical records. All subjects in the study received a 5 ml venous blood sample from a biotechnologist who was blind of their clinical atherosclerosis status. Blood samples were centrifuged and serum collected for the rapid screening test for hepatitis C virus infection.

Hepatitis C virus (HCV) infection was detected in all patients included using a rapid diagnostic orientation test. The test used was Hepatitis C Virus Test Strip® from Abon Biopharm (Hangzhou-China) (Sensitivity = 99.53%-100.0%; specificity = 99.15%-99.88%).

Subjects who tested positive for HCV were further tested with HCV confirmation serology by ELISA (Enzyme-linked immunosorbent assay) and a "Polymerase Chain Reaction" (PCR) for the determination of HCV viral load.

For subjects previously followed for chronic hepatitis C, treatment data as well as the latest assessment including the ELISA test and PCR were retrieved from the follow-up file.

Data analysis was performed using EpiData version 3.1 and Epi Info 7.1.5.2 software. Qualitative data were expressed in frequency and compared by the exact Fisher test. The quantitative data were expressed as means \pm standard deviation and compared by the Student T test for independent series. A value of $p < 0.05$ was considered statistically significant.

Informed consent was obtained from all study participants. Hepatitis C treatment and follow-up were offered to subjects who tested positive.

Results

Sociodemographic and clinical characteristics of the study subjects

During the study period, 105 subjects (53 cases and 52 controls) were included. Cases and controls were comparable on age, body mass index and all atheromatous risk factors outside of hypertension. Male predominance was found in cases (sex-ratio of 1.5) and female predominance in controls (sex-ratio of 0.5).

The socio-demographic characteristics and background of the included subjects are summarized in Table 1. Acute coronary syndrome was the most common clinical form of atherosclerosis in 94.3% of cases as shown in Table 2.

Prevalence of hepatitis C virus infection and association with

clinical atherosclerosis

Of the 105 subjects in the study, the HCV rapid screening test was positive in 4 (3.8%), including 2 cases (3.8%) and 2 controls (3.8%). There was no significant association between hepatitis C virus infection and the presence of clinical atherosclerosis ($p=0.68$). One of the two cases had an undetectable charge. Table 3 summarizes the results of the rapid screening test, ELISA HCV serology, PCR, viral load and HCV genotype in cases and controls.

	All (N=105)	Cases (N=53)	Controls (N=52)	p (cases vs controls)	
Age (years)	59.7 ± 11.0	59.1 ± 12.0	60.3 ± 9.9	0.56	
Weight (kg)	77.0 ± 14.6	76.5 ± 13.3	77.5 ± 15.8	0.7	
Height (m)	1.7 ± 0.1	1.7 ± 0.1	1.6 ± 0.1	<0.001	
BMI (weight/height ²) kg/m ²	28.3 ± 5.5	27.6 ± 4.8	29.0 ± 6.2	0.04	
Sex	Male	49	32	17	-
	Female	56	21	35	
	Sex-ratio	0.8	1.5	0.5	
Atherosclerosis risk factors	Hypertension	90 (85.7%)	40 (%)	50 (%)	0.002
	Diabetes	28 (26.7%)	17 (%)	11 (%)	0.14
	Dyslipidemia	23(21.9%)	13 (%)	10 (%)	0.33
	Smoking	6 (5.7%)	5 (%)	1(%)	0.10

Table 1: Hepatitis C virus infection and clinical atherosclerosis at University Hospital of Cotonou, socio-demographic characteristics of the study population.

	Number (N=53)	Fréquence (%)
Acute coronary syndrome	50	94.3
Obliterant arteriopathy of the lower limbs	1	1.9
Carotid atheroma	1	1.9
Ischemic stroke	1	1.9

Table 2: Hepatitis C virus infection and clinical atherosclerosis at University Hospital of Cotonou, clinical forms of atherosclerosis in cases.

	HCV Rapid Test	Serology ELISA HCV	PCR HCV	HCV viral load HCV en IU/ml (log)	Genotype HCV
Case n°1	Positive	Positive	Positive	2,605,967 (6.42 log)	2
Case n°1	Positive	Positive	Négative	undetectable	-
Control n°1	Positive	Positive	Positive	832,756 (5.92 log)	1
Control n°2	Positive	Positive	Positive	3 526 471 (6.55 log)	2

Table 3: Hepatitis C virus infection and clinical atherosclerosis at University Hospital of Cotonou, results of HCV Rapid Test, HCV ELISA serology, PCR, viral load and HCV genotyping, in cases and controls.

Discussion

In our series, the mean age of the subjects was 59.7 years ± 11.0 with no significant difference between cases and controls. Cases and controls were comparable across all conventional atheromatous risk factors outside of hypertension, which had a higher prevalence

among controls. Acute coronary syndrome was the most common clinical form of atherosclerosis in cases. HCV seroprevalence was identical among the cases and controls in our study (3.8%). This seroprevalence is close to 4.12% found for HCV among new blood donors in Benin in 2013 [16]. Thus, according to our results, there was no significant association between hepatitis C virus infection and the presence of clinical atherosclerosis.

Unlike our work, the results of a meta-analysis consistently showed that HCV infection was associated with an increased risk of cardiovascular and cerebral disease [17]. In particular, compared to subjects not infected with HCV, there is an increased prevalence of coronary artery disease and cerebrovascular disease among HCV-infected subjects [17]. The same observations were made by another meta-analysis including 22 published studies, which assessed cardiovascular mortality and atherosclerosis in HCV-infected patients [18]. Petta et al. [18] found that in this clinical context of HCV infection, the risk of cardiovascular disease and stroke occurred in 30% of cases. In this study, hypertension and diabetes mellitus had a significant impact on the risk of cardiovascular events and strokes.

However, this hypothesis was contradicted by the meta-analysis of Ambrosino et al. [17] who found an impact of cirrhosis on the risk of cardiovascular disease associated with chronic HCV infection. In particular, an increasing percentage of cirrhotics had a large difference in the occurrence of cardiovascular disease risk than controls. The interpretation of these results could be misleading: the fact that cirrhosis provides protection or accelerates atherosclerosis remains an unresolved controversy [17].

Thus, other authors believe that the prevalence of atherosclerosis and coronary artery disease has been considered lower in patients with hepatic insufficiency, or cirrhosis, than in the general population [19]. The hypothesis is that a favourable cardiovascular risk profile in cirrhotics could be attributed to one of the following factors: impaired coagulation, thrombocytopenia, platelet dysfunction, low blood pressure concentration and cholesterol levels [20,21]. However, the paradigm of low cardiovascular risk in cirrhotics is mainly based on post-mortem studies [19,22,23].

On the other hand, several factors can play a mediating role in the link between HCV infection and the risk of cardiovascular disease [24]. These include increased oxidation stress, altered iron homeostasis [25], induction of a liver disorder including steatosis leading to decreased insulin sensitivity and other related metabolic disorders [26]. These are also the activation of immunological and/or inflammatory abnormalities, the balance of disturbed cytokines [27] and viral replication in situ [28]. HCV receptors may be present in the cerebrovascular endothelium; thus HCV RNA has been observed in brain tissue from cells of HCV-infected individuals [29].

In addition, Boddi et al. [30] have demonstrated that HCV RNA is present in carotid plaques. Although it is difficult to prove the association between atherosclerosis and HCV infection as in our

work, results suggest that local active HCV infection could have an impact on the pathology of arterial wall cells [31].

Our study is the first to study this problem in a population in Benin. It presents as an essential limitation the low number of patients with a small number of cases of HCV infection found. Further work is therefore needed on a larger population, including comparing a large number of HCV-positive cases with non-HCV-positive controls with respect to the frequency of clinical atherosclerosis, at best in a longitudinal study.

Conclusion

HCV seroprevalence was identical in cases and controls, and close to that found in blood donors in Benin. This work has therefore failed to find an association between HCV infection and clinical atherosclerosis in the study population. However, the small size of our population has reduced the power of the study. A larger study, including a larger number of cases and controls, is needed to clarify these data.

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