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Assessment of carotid intima-media thickness and carotid plaque formation among patients with ischemic stroke and hepatitis C virus infection

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Abstract

Background: Cerebrovascular diseases are well known all over the world to be among the top list of the causes of death. One third of ischemic stroke could be regarded to plaque rupture and embolization. The actual mechanisms have not been exactly understood, but inflammation plays a pathogenic role. Patients with hepatitis C virus (HCV) proved to have a high level of inflammation. Replication of HCV within the brain endothelial cells and carotid plaques and, recently, the consideration of HCV as playing a role in risking for atherosclerosis rose the question of the role of HCV in cerebrovascular diseases.

Objective: Evaluating the role of infection with HCV among patients with stroke through assessment of carotid atherosclerosis.

Patients and methods: A cross-sectional study was carried out on 100 patients with ischemic stroke, aged 40–60 years, enrolled from the Neuropsychiatry Department of Suez Canal University Hospital. Patients were classified into 50 HCV-positive patients and 50 HCV-negative patients. All patients were assessed for HCV and the traditional risk of stroke as they were subjected to complete neurological examination, assessment of vascular risk factors, and a full extracranial neurovascular ultrasonography. Features evaluated were isolated increase of common carotid artery mean intima-media thickness (IMT) and extracranial atheromatous plaques.

Results: Intima-media thickness (IMT) was significantly higher in HCV-positive patients (1.04) than in HCV-negative patients (0.71). The percentage of plaque formation was insignificantly more frequent in HCV-positive patients (20%) than HCV-negative patients (10%). IMT and plaque formation were significantly increased in HCV-positive patients with high viremia. The multivariate analysis statistics concluded that infection with HCV was independently a risk factor for stroke.

Conclusion: Patients with HCV infection are at higher and earlier risk of stroke. The key mediator is inflammation. Lastly, researchers and clinicians should take these new findings into their consideration.

Keywords: HCV, Ischemic stroke, Carotid atherosclerosis

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Introduction

Hepatitis C virus (HCV) infection is a worldwide endemic disease, with estimated prevalence of 3% all over the world, resulting in 170–200 million infected persons worldwide [1]. Egypt has been considered as the highest epidemic area of HCV infection all over the world, with an estimated prevalence of 14.7%, resulting in 11,466,000 infected persons with rate of 6/1000 new infections each year [2]. Chronic HCV infection may cause hepatic, metabolic, and extra hepatic diseases [3, 4]. Also, it has been claimed that atherosclerosis risk is much higher among those subjects with HCV markers [5, 6]. Destabilization of the carotid atheromatous plaque may have the main role in the risk of developing stroke. The plaque rupture and erosion lead to thrombus and embolus formation, with the consequences of brain ischemic injury. This process is responsible for about 20 to 30% of ischemic stroke patients. Inflammation seemed to be the crucial arbitrator for plaque rupture [7].Taking into consideration that HCV positive patients showed high levels of systemic inflammation [8], and the finding of human brain endothelial cells which act like receptors for HCV entry and replication make us to believe in a possible direct vascular damage in those patients [9].

Aim

The aim was to evaluate the relationship between the infection with HCV and the carotid atherosclerosis among patients with ischemic stroke.

Patients

This descriptive cross-sectional study was performed in the Neuropsychiatry Department, Suez Canal University Hospital, Ismailia, Egypt. Patients with established diagnosis of ischemic stroke were included and categorized into two groups. Group 1 consists of 50 HCV-positive patients, and group 2 consists of 50 HCV-negative patients. We excluded patients with cardiac source of emboli, non-vascular causes of neurological disorder, connective tissue disease, patients with malignancies, systemic infection in the preceding 8 weeks, and whom neuroimaging techniques demonstrated the presence of intracerebral hemorrhage. We also excluded patients who suffer from diabetes mellitus (DM) or dyslipidemia at HCV-positive patients group in order to decrease the cofounders. Dyslipidemia is defined as (total blood cholesterol levels > 200 mg/dl, low density lipoproteins levels > 130 mg/dl, high density lipoproteins levels < 60 mg/dl, or triglyceride levels > 150 mg/dl [10]. This study was approved by the Suez Canal Faculty of Medicine Ethical Committee, and all participants signed informed consent before inclusion in the study.

Methods

All subjects included were subjected to the following:

A. Clinical assessment including thorough history taking and full general and neurological examination using the National Institutes of Health Stroke Scale (NIHSS) [11, 12]. The Model for End-Stage Liver Disease (MELD) score was used for assessing the severity of chronic liver disease [13]
B. Routine laboratory investigations including complete blood picture, erythrocyte sedimentation rate, C-reactive protein, fasting and postprandial blood glucose, liver function tests, renal function tests, and lipid profile. For all patients, HCV Ab seropositivity was assessed using ELISA assay, patients who were positive by ELISA were evaluated by PCR assay for serum HCV RNA positivity, and they subdivided into low and high viral load. Interpreting viral load test results, expressed as international units (IU/mL), low viral load is less than 800,000 IU/mL and high viral load is more than 800,000 IU/mL [14]
C. Electrocardiography and transesophageal echocardiography to detect cardiac source of emboli
D. CT scan and MRI of brain considered to support the clinical impression and to establish the diagnosis
E. Extra cranial carotid duplex study where carotid arteries was studied using a high resolution B-mode ultrasonography. The carotid arteries were studied by using a device (Philips HD11) with a linear probe (7 MHz) which is available at the Radiology Department of Suez Canal University Hospital

Position of the patient

The patient was in a recumbent position with head slightly extended and turned 10° to the opposite side. Using B-mode transverse scan of vessels to study the arterial wall morphology, we discovered intima-medial changes and existence of atheromatous plaques. Longitudinal section of the left and right common carotid artery, bulb, and the internal carotid artery (ICA) in each patient was scanned, and then evaluation of the intima-media thickness at the far wall of the common carotid artery (CCA) was done [15]. Estimation of the intima-media thickness was done with a computer-helped technique through the calculation of the difference between the first and the second interface (intima lumen and media adventitia) on the far wall of the common carotid artery in a plaque-free section which lies 10 mm below their bifurcations [16].

Each subject went through three measurements on both sides [17]. Maximum (outside the plaque) rather than mean values of IMT was considered. The average of IMT measurement on both sides was considered [18]. Carotid plaque was defined as the clearly identified focal

Table 1 Clinical characteristics among the HCV-positive and HCV-negative patients

	HCV-positive patients ($n = 50$)	HCV-negative patients ($n = 50$)	P value
Smoking *N* (%)	26 (52%)	30 (60%)	0.5
HTN *N* (%)	7 (14%)	15 (30%)	0.04*
Previous stroke *N* (%)	0 (0%)	8 (16%)	0.02*

*Statistically significant $P < 0.05$

thickening of the intima-media layer in the wall of the common carotid arteries, internal carotid arteries, or the carotid bulb, measuring 1 mm or more [19].

Statistical analysis

We gathered data processed using SPSS version 22 (SPSS Inc., Chicago, IL, USA). Quantitative data were presented as means ± SD while qualitative data were presented as numbers and percentages. Student t test was used to compare between the two means while chi-squared test was used to compare between the qualitative data and logistic regression linear model to identify factors independently associated with ischemic cerebral stroke. Odds ratio was calculated for factors independently associated with ischemic cerebral stroke. P value < 0.05 was set as statistically significant, and P value < 0.01 was set as statistically highly significant.

Results

Age of patients ranged from 41 to 64 years with the mean of 50.73 ± 7.1. There were 58 (58%) males and 42 (42%) females. The mean age of patients with HCV-positive was 45 ± 10 years while it was 49 ± 5 years for HCV-negative patients. There were 27 males (54%) and 23 females (46%) patients in HCV-positive patients, versus 31 males (62%) and 19 females (38%) patients in HCV-negative patients. There was no statistically significant difference between both groups regarding age and sex (P value = 0.1 and 0.4 respectively).

Vascular risk factors among both groups showed a higher preponderance among HCV-negative patients than HCV-positive patients. On the other hand, there was no statistically significant difference between the two groups regarding smoking status and NIHSS score (Tables 1 and 2).

Regarding the extra-cranial duplex findings among HCV-positive patients and HCV-negative patients, the carotid intima-media thickness (IMT) was statistically significantly higher among those patients with HCV-positive than those with HCV-negative (Tables 3 and 4). Also, plaque formation in HCV-positive patients was more frequent than in HCV-negative patients (10%). However, the difference is statistically non-significant (Table 5).

Plaques were significantly more frequent at the CCA and ICA in HCV-positive patients and at the carotid bulb in HCV-negative patients (P value < 0.001). There was no significant difference detected between HCV-positive patients and HCV-negative patients regarding plaque homogeneity, echogenicity, or surface (P value > 0.05) (Table 6).

Regarding the relation between the severity of the hepatitis C virus infection and the severity of the atherosclerosis among patients with HCV-positive, there was a difference between patients with low and high viremia as those with high viremia had more significant increase in IMT and also in plaque formation. There was no significant relation between MELD score and severity of atherosclerosis (Tables 7 and 8).

Multiple logistic regression analysis including other confounding risk factors, male sex, smoking, hypertension, dyslipidaemia, diabetes mellitus, and hepatitis C virus of atherosclerosis, revealed that HCV infection was positively and independently associated with isolated elevation of CCA mean IMT with an OR of 2.07 (95% CI 1.50–2.85) and (P value < 0.0001) (Table 9).

Multiple logistic regression analysis including other confounding risk factors, male sex, smoking, dyslipidaemia, hypertension, diabetes mellitus, and hepatitis C virus of atherosclerosis, revealed that HCV infection was positively and independently associated with presence of carotid plaques with an OR of 5.61 (95% CI 2.06–15.26) and (P value < 0.001) (Table 10).

Table 2 NIHSS score among the HCV-positive and HCV-negative patients

NIHSS	HCV-positive patients ($n = 50$)	HCV-negative patients ($n = 50$)	P value
< 5	3 (6%)	2 (4%)	0.8
5–15	39 (78%)	43 (86%)	0.5
> 15	8 (16%)	5 (10%)	0.6

NIHSS National Institutes of Health Stroke Scale

Table 3 Carotid intima-media thickness difference among HCV-positive and HCV-negative patients

	HCV-positive patients ($n = 50$)	HCV-negative patients ($n = 50$)	P value
IMT (in mm) (mean ± SD)	1.04 ± 0.23	0.71 ± 0.13	< 0.001**

IMT intima-media thickness, *mm* millimeter
**Statistically highly significant $P < 0.001$

Table 4 Intima-media thickness difference among HCV-positive and HCV-negative patients

	HCV-positive patients *N* (%)	HCV-negative patients *N* (%)	P value
IMT < 1 mm	10 (20%)	34 (68%)	< 0.001**
IMT > 1 mm	40 (80%)	16 (32%)	< 0.001**

IMT intima-media thickness, *mm* millimeter
**Statistically highly significant $P < 0.001$

Table 5 Plaque formation among HCV-positive and HCV-negative patients

	HCV-positive patients ($n = 50$)	HCV-negative patients ($n = 50$)	*P* value
Plaques *N* (%)	10 (20%)	5 (10%)	0.1

Discussion

The purpose of this study was to detect the relationship between HCV infection and carotid atherosclerosis in patients with ischemic stroke. This was achieved by determining whether HCV infection constitutes a significant difference in the risk of developing carotid atherosclerosis or not and by detecting the proportion and pattern of carotid atherosclerosis in HCV-infected patients. In this study, the main focus was the data analysis for measurable findings in the cardiovascular system. So, HCV infection among stroke patients was independently studied regardless the effect of the other risk factors and confounders of stroke. We also excluded patients who suffer from DM or dyslipidemia in the HCV-positive patients group in order to decrease the confounders.

Many studies found a positive link between HCV infection and the important risk factors for stroke including the type 2 diabetes mellitus among other metabolic syndromes [20–23]. This study excluded diabetes to make sure to evaluate the effect of HCV infection in stroke furthermore independently.

In this study, carotid intima-media thickness showed higher statistically significant difference among those HCV-positive patients than those with HCV-negative (*P* value < 0.001). IMT > 1 mm was statistically significantly more frequent among HCV-positive patients (80%) than among HCV-negative patients (32%) (*P* value < 0.001), which agreed with Boddi and his colleagues who found that IMT > 1 mm was highly statistically more prevalent among anti-HCV-positive subjects than among controls [24]. Meanwhile, Targher and his colleagues stated that HCV infection was an independent predictor of the increased carotid IMT [25].

Table 6 Plaque morphology among HCV-positive and HCV-negative patients

Plaque morphology	HCV-positive patients	HCV-negative patients	*P* value
Location			
Common carotid	6 (60%)	1 (20%)	< 0.04*
Carotid bulb	1 (10%)	4 (80%)	< 0.03*
Internal carotid	3 (30%)	0	< 0.05*
Homogeneity			
Homogenous	7 (70%)	3 (60%)	0.5
Heterogeneous	3 (30%)	2 (40%)	
Echogenicity			
Echogenic	6 (60%)	4 (80%)	0.09
Echolucent	4 (40%)	1 (20%)	
Surface			
Regular	6 (60%)	3 (60%)	0.07
Irregular	3 (30%)	2 (40%)	
Ulcerated	1 (1%)	0	

*Statistically significant $P < 0.05$

Table 7 Relation between MELD score, viral load, and IMT among HCV-positive patients

	IMT		*P* value
	< 1	> 1	
MELD score			
0 to < 9	31	23	0.6
9–12	17	7	
> 12	13	9	
Viral load			
Low	9 (23.1%)	5 (8.2%)	< 0.05*
High	8 (13.1%)	28 (71.8%)	

MELD The Model for End-Stage Liver Disease, *IMT* intima-media thickness
*Statistically significant $P < 0.05$

Regarding the frequency and the intensity of infection, a 2.5-year follow-up study on several serological markers of infectious agents showed that individuals who had been exposed to an increased number of infectious pathogens had an elevated risk of atherosclerosis [26].

In the current study, we found that HCV-positive patients with high viral load were more prone to the increase in carotid IMT (71.8%) than those with low viral load (5%). This finding is supported by Adinolfi and his colleagues who found that HCV infection is a risk factor for early formation of carotid atherosclerosis through the viral load and steatosis with the modulation of the atherogenic factors such as inflammation [6]. Lee and his colleagues also, in a community-based prospective cohort study, concluded that chronic HCV infection is an independent risk predictor of cerebrovascular deaths, showing a severity-dependent cerebrovascular mortality with increasing serum HCV RNA level [27].

Table 8 Relation between MELD score, viral load, and plaque formation among HCV-positive patients

	Plaque	*P* value
MELD score		
0 to < 9	4	0.5
9–12	4	
> 12	2	
Viral load		
Low	3	< 0.05*
High	7	

MELD The Model for End-Stage Liver Disease
*Statistically significant $P < 0.05$

Table 9 Predictors for intima-media thickness

	Odds ratio (95% CI)	*P* value
Sex (male)	1.01 (0.72–1.42)	0.95
Smoking	1.20 (1.03–1.41)	< 0.05*
Dyslipidaemia	1.02 (0.92–1.13)	0.72
hypertension	1.02 (0.79–1.33)	0.85
Diabetes mellitus	1.01 (0.87–1.17)	0.91
Hepatitis C virus	2.07 (1.50–2.85)	< 0.0001**

Odds ratio derived from logistic regression analysis including all the variables
CI confidence interval
*Statistically significant $P < 0.05$
**Statistically highly significant $P < 0.001$

Regarding carotid plaque formation, we found that the percentage of plaque formation in HCV-positive patients was more frequent (20%) than in HCV-negative patients (10%). However, the difference is statically non-significant (*P* value > 0.05). Ishizaka and his colleagues found that individuals seropositive for HCV core protein had 5.6 times risk of developing carotid plaque [28]. Aslam and his colleagues also, in their research review, concluded the higher incidence of carotid atherosclerotic plaques among HCV-positive patients than HCV-negative individuals [29].

Regarding presence of a relation between stroke severity and atherosclerosis, statically significant difference have been found between the two groups of patients (HCV-positive and HCV-negative), according to the IMT, in those patients whose NIHSS stroke scale ranged from 5 to 15 only.

In contrast, regarding relation between HCV severity and atherosclerosis in HCV-positive patients, there was a difference between patients with low and high viremia as those with high viremia had more significant increase in IMT and also in plaque formation as we discussed before, while there was no significant relation between MELD score and severity of atherosclerosis.

The data of this study showed that HCV infection is a risk factor associated with stroke after controlling for the major traditional risk factors (O.R 2.07, 95% C.I. 1.50–2.85, $P < 0.0001$). The results of our study mirror those recently published by Adinolfi and his colleagues who demonstrated, in a retrospective case control study, that HCV infection is associated with an increased risk of ischemic stroke [30]. And, similar to that published by Liao and his colleagues, who demonstrated, in a large prospective population-based cohort, that the cumulative risk of stroke for HCV positive subjects was significantly higher than those without HCV infection [31].

Table 10 Predictors for carotid plaques

	Odds ratio (95% CI)	*P* value
Sex (male)	2.76 (2.41–3.15)	0.01*
Smoking	1.06 (0.92–1.22)	0.08
Dyslipidaemia	1.01 (0.30–1.36)	0.13
hypertension	1.37 (0.86–2.18)	0.17
Diabetes mellitus	1.24 (0.92–1.68)	0.15
Hepatitis C virus	5.61 (2.06–15.26)	< 0.001**

Odds ratio derived from logistic regression analysis including all the variables
CI confidence interval
*Statistically significant $P < 0.05$
**Statistically highly significant $P < 0.001$

Conclusion

This study concluded that patients with HCV infection are at higher and earlier risk of stroke. The key mediator is inflammation. Lastly, researchers and clinicians should take these new findings into their consideration.

Abbreviations

CCA: Common carotid artery; DM: Diabetes mellitus; ELISA: Enzyme-linked immunosorbent assay; HCV: Hepatitis C virus; HCV Ab: Hepatitis C virus antibody; HCV RNA: Hepatitis C virus ribonucleic acid; ICA: Internal carotid artery; IMT: Intima-media thickness; MELD score: Model for End-Stage Liver Disease; NIHSS: National Institutes of Health Stroke Scale; PCR: Polymerase chain reaction; U/S: Ultrasonography

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Availability of data and materials

Availability of data and materials: the data can be publicly available at the Faculty of Medicine, Suez Canal University.

Authors' contributions

OA carried out the study conception and design, participated in its design and coordination, and drafted the manuscript. AY carried out the design of the study, carried out the analysis and interpretation of data, and helped to draft the manuscript. AR participated in the sequence alignment, interpretation of data, and drafting of the manuscript. MD participated in the acquisition of data and performed the statistical analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics committee of Suez Canal Faculty of medicine in April 29, 2015. Committee Number: 2413 An informed consent was taken from all the participants in the study.

Consent for publication

Participants signed an informed consent for publication.

Competing interests

The authors declare that they have no competing interests (financial or non-financial).

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