Characteristics of ischemic stroke in asymptomatic hepatitis C virus positive patients

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Abstract: Background and aim of the study: Cerebrovascular diseases are leading cause of death worldwide. Acute ischemic cerebrovascular events, including ischemic stroke (IS) , transient ischemic attack, and lacunar syndromes, have been reported in hepatitis C virus infected patients. Various surveys were designed to study the associations and pathophysiology of ischemic stroke in patients with hepatitis C virus infected patients. The purpose of our work was to determine the Characteristics of ischemic stroke in hepatitis C virus infected patients. **Patients and Methods:** Forty ischemic stroke patients with positive hepatitis C virus antibodies compared with 20 ischemic stroke patients with negative hepatitis C virus antibodies. We examined traditional vascular risk factors, stroke severity, carotid atherosclerosis, and a range of radiological and laboratory markers. **The results:** IS patients with positive hepatitis C virus (HCV) antibodies were significantly younger (62.8±7.7, versus 67.3±7, P= 0.007). The risk of stroke recurrence is significantly higher in ischemic stroke with positive HCV antibodies (32.2% versus 5%, P=0.028), with larger numbers (P=0.026) but smaller sizes (4.544 cm3 versus 17.492 cm3, P=0.007) in addition to significantly higher association with carotid atherosclerosis (73.3% versus 28.5%., P=0.047) and less severe stroke (P=0.028) than those with negative hepatitis C virus antibodies. **Conclusion:** Our results show that hepatitis C virus infection can accelerate atherosclerosis and leading to stroke at a relatively younger age with increased incidence of stroke recurrence and usually associated with small lacunar syndromes and less severe stroke.
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Introduction

The worldwide prevalence of hepatitis C virus (HCV) is to be 170 million individuals (1). Egypt receives the highest prevalence of hepatitis C virus in the world with more than 14.7% of the Egyptian population have HCV infection (2).

In HCV infected patients , acute vascular events, including ischemic stroke, transient ischemic attack, and lacunar syndromes have been reported (3), these ischemic events may be the presenting manifestation of HCV infection in some cases (4).

Some factors may explain the associations and pathophysiology of ischemic stroke in patients with HCV infected patients. First the presence of anticardiolipin antibodies may play an important role in acute ischemic stroke (5). Second , hypertension (6), type 2 DM is thought to be prevalent in chronic HCV patients (7). Besides, it is well documented that HCV infection, especially in those with elevated hepatitis C viral load has a part in the development of carotid atherosclerosis (8),(9). Finally HCV may be an indirect risk factor of stroke by occlusive vasculopathy and vasculitis which are well known in HCV patients (10).

Aim of the work

The purpose of this work was to ascertain the characteristics of ischemic stroke in HCV infected patients.

Patients and methods

This is a comparative study, comparing ischemic stroke patients with and without positive HCV antibodies. We prospectively compared data from consecutive ischemic stroke patients with (group A) and without (group B) HCV antibodies. Patients in the study were admitted to Department of Neurology, Sohag University Hospital in the period between June 2013 and May 2014. Stroke was defined according to the definition of the World Health Organization as the rapid onset of a new persistent neurological deficit attributable to an obstruction in cerebral blood flow with no apparent non-vascular cause (11). The work was approved by the Medical Research, Ethical Committee of Sohag Faculty of Medicine. All participants signed written consents. Patients were excluded from the study if they had a hemorrhagic stroke, transient ischemic attack (TIA), previous diagnosis and/or current ischemic heart disease,

cardiac valvular disease, congestive heart failure, cardiomyopathies, and advanced renal or liver disease.

All patients were subjected to full history taking, complete medical and neurological exam. Patients with past or current history of smoking were categorized as smokers. Hypertension was defined as self-report of hypertension with antihypertensive medication use, and/or systolic blood pressure greater than or equal to 140 mm Hg, and/or diastolic blood pressure greater than or equal to 90 mm Hg. Diabetes was defined as being on treatment for diabetes by self-report and/or having a fasting glucose level greater than or equal to 126 mg/dL. Hypercholesterolemia was defined as a cholesterol level of more than 200 mg/dL or in the presence of a specific treatment. Hypertriglyceridemia was defined as a triglyceride level of more than 200 mg/dL. Admission stroke severity was assessed by the Scandinavian Stroke Scale (SSS). The SSS is a validated neurological stroke scale that evaluates stroke severity on a score from 0 to 58, with lower scores indicating more-severe strokes (12).

Approximately 10 ml venous blood was drawn from each study included in this study by a clean venipuncture under aseptic conditions and divided into EDTA, sodium citrate 3.8% and plain vacutainer tubes. The sera were separated by centrifugation after clotting and were stored at - 20 °C until analyzed. Biochemical assays for serum alanine Aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (Bil. T), direct bilirubin (Bil. D), albumin, cholesterol, triglyceride (TG) and creatinine were determined by Cobas c311 Chemistry Analyzer System (Roche Diagnostics, GmbH, Mannheim, Germany). Erythrocyte sedimentation rate and Complete Blood Count (CBC): CBC was done by Cell-Dyn 3700 (Abbott Laboratories, Diagnostic Division, IL, USA). Prothrombin time - INR was studied with a Sysmex CA-1500 coagulometer (Siemens, Healthcare Diagnostics Inc, USA). Serological testing for both anti-HCV and HBsAg were evaluated by the Architect i1000SR system (Abbott Laboratories, Diagnostics Division, IL, USA).

CT brain was done for all patients to evaluate the site and size of ischemic lesion. The size of the lesion was measured according to radiological parameters. The size was detected by the largest diameter (A) of the infarct and its largest perpendicular diameter (B) was measured. The third, vertical diameter (C) was determined by summation the thicknesses of the slices in which the lesion was visible. Infarct volume was calculated according to the formula: Size = 0.5x A x B x C (13). Echocardiography was performed for all patients. Carotid Doppler was done by high-resolution B-mode ultrasonography equipped with a 7.5 MHz linear-array transducer. Extracranial carotid arteries were scanned bilaterally along the anterior, lateral, and posterior axes, in transverse and longitudinal planes. Patients were lying in a supine position with the neck was in mild Hyperextension position as well as almost 45 degree rotation away from the examined side. Measurements were taken in on frozen images of carotid arteries at the level of the common carotid arteries, internal carotid arteries and bulb tracts. On the screen displaying the frozen image, 2 cursors were positioned on the boundaries of the intima and media respectively. The distance between the cursors was recorded to the nearest 0.1 mm. Intima-media thickness (IMT) of the common carotid arteries was considered as the distance between the lumen-intima interface and the leading edge of media-adventitia interface (14). Thus, only the intima which appears as echogenic layer and the media which appears as echo-poor layer were included in the measurement (15). IMT measurements of the carotid artery were taken in triplicate for each site and the mean value was calculated and recorded. In agreement with the Mannheim Carotid Intima-Media Thickness Consensus, IMT >1 mm was regarded as a cut-off value for carotid atherosclerosis (CA) given that it is associated with a 3-4 fold increased risk of subsequent ischemic stroke (16). Plaques were defined as protrusions into the vessel lumen of at least 1.5 mm, as assessed from the boundary line between the adventitial and median layers. The term "CA" was applied to show the overall occurrence, e.g., increased IMT (>1 mm) and /or plaques.

Statistical data analysis:

The data were analyzed by Statistical Package for the Social Sciences (SPSS version 20) for windows. Continuous data were expressed as mean ± SD, and categorical data were expressed as numbers and percent. Comparisons of differences between two groups were executed by the Student's t-test for the continuous data, Chi-square test for categorical data. P values equal or less than 0.05 were considered statistically significant.

Results:

During the period of the study, the inclusion criteria were applied on 60 ischemic stroke (IS) patients (30 males and 30 females). Forty patients were categorized as group A and 20 patients as group B. The characteristics of the 60 subjects included in the study are reported in Table 1. Our results showed that the IS patients with positive HCV antibodies (group A) were significantly younger than those with negative HCV antibodies (group B). The mean age of the first group was 62.8±7.7, while in group B was 67.3±7 (P = 0.007). No sex difference was reported between the 2 groups. Smoking was non significntly more prevalent in group A than in group B (P=0. 1).

Stroke recurrence was significantly higher in group A (P = 0.028). No significant differences were detected between both groups regarding the prevalence of diabetes mellitus or hypertension. Stroke severity, measured by SSS, was significantly higher in patients with negative HCV antibodies (P=0.028). Carotid atherosclerosis was significantly more prevalent among group A patients (p = 0.047) (Figure 1). Stroke patients with HCV antibodies had significantly higher number, but smaller sizes of brain ischemic lesions (p = 0.003, p = 0.047 respectively) (Table 2). Stroke patients with HCV infection showed significantly higher serum levels of total serum bilirubin (P=0.048), direct bilirubin (P=0.034), ALT (P=0.009), AST (P=0.040), triglycerides (P=0.010) and ESR (P=0.020) than those without CV infection (Table 3).

Discussion:

This study revealed that stroke patients with positive HCV antibodies were significantly younger, carry higher risk of recurrence, with larger numbers but smaller sizes of ischemic lesions, with significantly higher association with CA and less severe stroke than those with negative HCV antibodies. In a large prospective population-based cohort, Liao and colleagues (17) demonstrated that the cumulative risk of stroke is significantly higher for HCV positive subjects. Similarly , a community-based prospective cohort study reported that chronic HCV infection with increasing serum HCV RNA level is not only a predictor of stroke severeity but also an independent risk predictor of stroke deaths (18).

Adinolfi and colleagues (19) reported that the prevalence of HCV infection in stroke patients is significantly higher and this finding coupled with those reported by others(17, 18) complete the HCV-stroke puzzle (high prevalence, incidence and mortality) that strongly suggests a strict association between chronic HCV infection and stroke event.

Table 1. Characteristics at the admission of the 60 patients included in the study

	Group A IS with HCV +ve antibodies	**Group B** IS with HCV-ve antibodies	P-value
Number of cases	40	20	
Age, M±SD	62.8 ±7.7	67.3± 4.6	0.007
Males no.(%)	22 (55%)	8 (40%)	0.44
Smoking	12 (30%)	5 (25%)	0.1
DM	17 (42.5%)	7 (35%)	0.5
Hypertension	30 (75%)	13 (65%)	0.4
Previous CVS	13 (32.5%)	1(5%)	0.028
SSS	38.2 ± 13.26	25.3 ± 17.2	0.028

IS: ischemic stroke, HCV: hepatitis C virus, DM: diabetes mellitus, CVS: cerebrovascular stroke, SSS: Scandinavian Stroke Scale

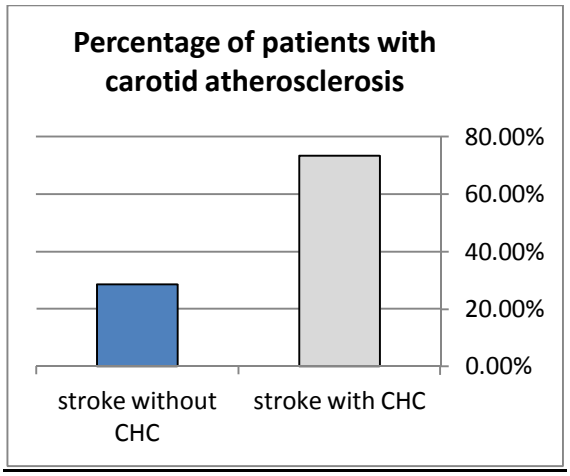

Figure (1): Percentage of patients with carotid atherosclerosis in both groups.

Table 2: Radiological characters of ischemic lesions in both groups

		Group A	Group B	Total	P value
Number of lesions	1	26	20	46	0.026
	>1	14	0	14	
Total		40	20	60	
Mean size of infarction		4.544 cm^3	17.492 cm^3		0.007

HCV: hepatitis C virus

Table (3): Laboratory findings in both groups

	Group A		Group B		P value
	Mean	SD	Mean	SD	
Total bilirubin	1.11	0.755	0.745	0.394	0.048
Direct bilirubin	0.587	0.512	0.336	0.202	0.034
ALT	45.775	33.801	39.85	9.298	0.009
AST	47.425	34.254	37.75	12.628	0.040
Albumin	3.269	0.707	3.48	0.726	0.173
Cholesterol	180.675	59.692	184.95	61.659	0.813
Triglycerides	205.65	105.566	167.75	62.08	0.010
Platelets	221.32	116.416	175.075	50.35	0.094
Creatinine	1.295	1.317	2.08	2.375	0.053
WBCs	9.258	3.795	7.537	3.349	0.134
PT	13.154	1.818	13.15	1.312	0.255
PC	82.108	14.663	83.45	11.814	0.513
INR	1.1605	0.152	1.159	0.169	0.315
ESR	36.50	30.31	15.8	16.694	0.020

ALT: alanine transaminase, AST: aspartate transaminase, PT: prothrombin time, PC: prothrombin concentration, ESR: erythrocytic sedimentation rate, WBCs: white blood cells, INR: international normalization ratio

The present work revealed that stroke patients with HCV were significantly younger than those without. This is in accord with a study by Adinolfi and colleagues who reported that HCV is a hazard element for an earlier stroke. It is important to underline that such ischemic event occurs despite HCV infected patients showed a more favorable risk profile such as lower lipid levels, lower prevalence of hypertension and of the male sex; in addition, the ischemic event in

anti-HCV positive patients occurs in younger age than those with anti-HCV negative. The data strongly support a direct role of HCV in determining conditions that favor ischemic cerebral events (19).

Stroke recurrence, in our study, was more common in patients with positive HCV antibodies. We found that the history of previous ischemic stroke was significantly higher in those with positive HCV antibodies than those without (P=0.015). This data from patients history is enforced by brain CT findings, which showed significantly higher number of previous cerebral infarctions in patients with positive HCV antibodies than those without (P = 0.026). This is in agreement with Fuckar and colleagues (6) and Lee and colleagues (18) who concluded that HCV is a risk factor for stroke recurrence. The authors of these previous studies reported that, this may be due to enhancement of the effect of other risk factors like hypertension or directly by the vasculitic changes of small brain vessels associated with HCV infection(6, 18).

In our study, we found that stroke patients with positive HCV antibodies showed significantly higher serum triglycerides (p = 0.006), and insignificantly lower serum cholesterol (p = 0.8) when compared to stroke patients with negative HCV antibodies. In 2001, Serfaty (20) reported that serum cholesterol concentration was significantly lower in HCV patients than in controls. Another study (21) has shown that patients with HCV-3 infection have age-adjusted hypocholesterolemia and more frequent hepatic steatosis. Moreover, Adinolfi and colleagues (22) and Butt and colleagues (23) reported that stroke patients with CHC had lower levels of cholesterol. The extent of liver steatosis is inversely related to the serum cholesterol concentrations, which suggests that a common pathway may underlie this metabolic disturbance (24, 25). In a Japanese study,(26) infection by HCV genotype-1b also induced a higher degree of hypocholesterolemia and hypobetalipoproteinaemia than HBV infection. The cause of this interaction is unknown, but the low-density lipoprotein receptors have been proposed as the recognition receptor for HCV entry in hepatocytes (27, 28).

One of the most important findings in the current study was an increased prevalence of carotid atherosclerosis in stroke patients with positive HCV antibodies than those without. This data agrees with the findings of previous studies (29-32), the largest one of them showing that HCV infected subjects had a significant higher prevalence of atherosclerosis despite being younger and having a more favorable cardiovascular risk profile (23). In 2012, Adinolfi and colleagues (22) reported that CHC patients had a significantly higher prevalence of CA compared with a matched control population (53.7% vs 34.3%). Furthermore, amongst the younger CHC patients (e.g. <50 years old) about 34% showed CA versus (16.0%) in the control group and a significant proportion (24.1%) had plaques, which was a rare event in the control group (3.9%). Their data supported the view that chronic HCV infection predisposes prematurely to the development of CA and of advanced lesions despite the more favorable cardiovascular risk profile featuring lower lipid levels, lower prevalence of metabolic syndrome and possible a lower prevalence of hypertension (33).

Several previous findings contributed to advance the understanding of pathogenic mechanisms linking HCV infection with early and advanced atherosclerosis. Serum HCV RNA levels were found to be independently associated with CA, in particular with both early phases of IMT lesion and advanced phase of plaques (22). In 2010, HCV RNA sequences were isolated inside carotid plaques and it was indicated that HCV replicates within CA (9). Taken together, these findings support a direct pro-atherogenic action of HCV, which could contribute per se to premature arterial ageing (9). An interesting previous finding is the demonstration that HCV patients with steatosis, irrespective of HCV genotype, age, gender and degree of histological liver damage, carried the highest prevalence of atherosclerosis (77.7%) (22). Moreover, HCV-related steatosis was an independent risk factor for atherosclerosis. HCV related steatosis has a good predictive ability to atherosclerosis with a good specificity and sensitivity (22).

The significantly higher serum triglycerides among HCV positive stroke patients, found in our study, could explain the increased prevalence of carotid atherosclerosis in this group. This is in agreement with Adinolfi and colleagues (22) who reported that higher levels of serum triglycerides and not serum cholesterol were significantly associated with carotid atherosclerosis in CHC patients.

The data of the present study show that HCV patients with stroke had had a significant higher level of ESR. These data strongly support the hypothesis that chronic HCV infection increases the risk of ischemic stroke through higher systemic inflammatory levels (19). It is evident that the instability of atheromatous plaque is at the base of ischemic events. It is also well known that inflammation play a major role in the instability of plaque (34). It has been suggested that infectious agents may induce atherosclerosis by inflammatory stimuli either locally within vascular wall or systemically through inflammatory mediators (35).

In this context, it has been demonstrated that HCV lives and replicates within carotid plaque (9) and

the virus enters and replicates inside human brain endothelial cells (36). Moreover, it has been demonstrated that HCV infection is associated with atherosclerosis by increasing local and systemic inflammation (37-39).

Adinolfi and colleagues (19) reported that HCV patients with stroke had significantly higher serum levels of inflammatory markers than negative ones; in particular HCV positive patients had significant higher levels of ESR, CRP and serum fibrinogen.

They also reported that, considering that HCV replicate within endothelial cells and within plaque, it is likely that in HCV infection a local inflammation of vascular endothelia and/or within plaque may occur. Such chronic inflammatory condition could promote not only the development of atheromas, but also its destabilization and, therefore, a higher risk of occlusive or embolic stenosis (19).

The present study revealed that the stroke severity was significantly lower in patients with positive HCV antibodies. In agreement with previous studies, HCV is more likely to cause small vessel disease and lacunar infarctions by its vasculitic changes on small brain vessels (3, 6).

Conclusion:

Our results show that HCV infection can accelerate atherosclerosis and leading to to stroke at a relatively younger age, with increase incidence of stroke recurrence and usually associated with small lacunas and less severe stroke.

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