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Hepatitis C Viral Load as a Predictor of Short Term Outcome of First-Ever Acute Ischemic Stroke

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Abstract

Background: Cerebrovascular disease is a great health burden. Hepatitis C Virus (HCV) infection has a role in the development of carotid atherosclerosis and recently associated to poor outcome in patients with stroke.

Aim of Study: The aim of this work was to investigate the prognostic value of HCV viral load on acute first-ever ischemic stroke outcome.

Patient and Methods: Sixty patients diagnosed with acute stroke were enrolled and divided into 41 patients with and 19 without chronic HCV. Stroke severity was assessed and correlated with HCV viral load which was determined By RT-PCR. The morphological and functional status of the liver was evaluated by ultrasonography and laboratory investigations including liver function tests.

Results: The outcome was favorable in 35% and unfavorable in 65%. The high level of HCV RNA in stroke patients was found to be an independent predictor of stroke outcome after controlling for age, hypertension, DM and stroke severity. Patients who died had significantly higher levels of HCV RNA than survivors.

Conclusion: High viremia is an independent predictor of short term outcome of first ever stroke.

Key Words: *Stroke – Chronic HCV – Risk factor – Outcome.*

Introduction

HEPATITIS C Virus (HCV) infection is a worldwide problem affecting about 185 million people with the highest prevalence been reported from Egypt **[1,2]**. Cerebrovascular disease is a great health burden in most industrialized countries **[3]**. Ischemic stroke is one of extrahepatic manifestations of HCV infection **[4]**.

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Cigarette smoking, alcohol consumption, obesity, hyperlipidemia, hypertension, and diabetes are considered traditional risk factors for ischemic stroke with emergence of new risk factors including infectious agents **[5,6]**.

To the best of our knowledge studies on the effect of viral load on stroke severity and outcome are lacking.

To further elucidate the relationship between HCV infection and ischemic stroke outcome, we conducted this study to investigate the predictive value of HCV viral load in assessing stroke short term outcome.

Patients and Methods

Design:

A prospective study was carried out with acute first-ever (occurring for the first time during the patient's lifetime) ischemic stroke patients to evaluate the association between HCV RNA viral load measured by RT-PCR (Real Time Polymerase Chain Reaction) and short-term outcome of stroke.

The study was approved by the Ethics Committee of Sohag Faculty of Medicine, Sohag University and written informed consents were obtained from all participants.

Study subjects:

Two hundred and ten patients admitted to Neurology Department Sohag University Hospital, were prospectively enrolled from October 2014 to July 2015. Of them, 60 patients were attended for first-ever acute ischemic stroke, diagnosed with focal neurological signs or symptoms thought to be of vascular origin that persisted for more than

24 hours [7], confirmed by brain Computed Tomography (CT). Those with clinical data corresponding to stroke with normal brain CT-Scan result was also considered as ischemic stroke Fig. (1).

Stroke severity was measured by the Scandinavian Stroke Scale (SSS) and categorized according to Stroke Unit Trialists' Collaboration into mild (43-58); moderate (26-42) and severe (0-25) [8].

Glasgow coma scale was used to assess conscious level of the patient and was graded as mildly disturbed (GCS=13-15), moderately disturbed (GCS=9-12), severely disturbed (GCS ‹_8) [9].

The short-term outcome (within 3 months of admission) was determined using the modified Rankin Scale (mRS) which is graded from 0 to 6 points [10] applied within the first twenty-four-hours of admission (baseline) and after three-month followed-up.

The outcome was assessed by routine follow-up or by using telephone interviews with the patients or their relatives. Patients were allocated into two groups: mRS <3 was labeled as favorable outcome or independence (no symptoms/mild disability) and those with mRS ›_3 were labeled as unfavorable outcome or dependence (moderate/severe disability) [11,12].

All patients were managed using a standardized protocol adapted from international guidelines for managing acute ischemic stroke and none of them received thrombolytic therapy.

Exclusion of patients was made according to the following criteria: 15 patients having an acute transient ischemic attack, TIA; 39 patients having recurrent stroke; 53 patients having renal affection with Creatinine > 1.2mg/dl); 14 patients having decompensated liver cirrhosis; 20 patients having an Intracerebral Hemorrhage (ICH); 9 patients having Hepatitis C and B and lastly 3 patients having urinary tract infection. There are three overlapping patients; 2 patients having both recurrent stroke and renal impairment and 1 patient having ICH and renal impairment Fig. (1).

Demographic and clinical data with recording of traditional stroke risk factors before the inclusion in the study were obtained.

Each patient was subjected to the following; full medical and neurological evaluation including age, sex, traditional stroke risk factors and history of exposure to previous operations or blood transfusion (for Hepatitis C Virus and hepatitis B virus) with assessment of patients with chronic hepatic disease for the presence of hepatomegaly, splenomegaly, manifestations of liver cell failure such as jaundice, ascites, and lower limb oedema.

Assessment of blood pressure; high blood pressure was defined as; use of anti-hypertensive drugs or persistently elevated blood pressure (>140/90 mmHg) on admission.

Diabetes mellitus was defined as; use of hypoglycemic agents or a fasting plasma glucose of >126mg/dl (after no caloric intake for at least 8 hours) or, casual plasma glucose >200mg/dl [13].

Abdominal Ultrasonography (U/S): Patients are subjected to U/S examination to assess liver size, surface, echogenicity, detect hepatic focal lesion(s) and ascites.

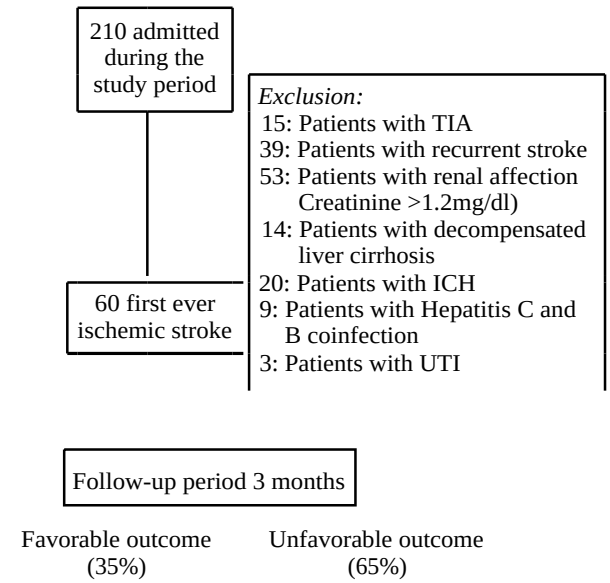

Fig. (1): Flowchart of study participants.

Laboratory assays:

About 1 0ml venous blood was withdrawn from each subject included in this study by a clean vein puncture under aseptic conditions.

The following investigations are performed:

A- Biochemical assays for blood glucose, creatinine, albumin, Alanine Transferase (ALT), Aspartate Transferase (AST), cholesterol and Triglyceride (TG) were determined by Cobas c311 Chemistry Analyzer System (Roche Diagnostics GmbH, Indianapolis, IN, USA).

B- Complete Blood Count (CBC): CBC was done by CELL- DYN 3700 (Abbott Laboratories, Diagnostics Division, Abbott Park, IL, USA).

C- Prothrombin concentration was done by Thrombol-S Kit using Sysmex CA-1500 fully auto-

mated coagulometer (Siemens Healthcare GmbH, Laboratory Diagnostics, Marburg, Germany).

D- Erythrocyte sedimentation rate.

E- Hepatitis markers; HCV antibodies and HBs Ag were detected by Architect i1000SR system (Abbott Diagnostics, USA).

F- Quantitative Real time PCR for the detection of HCV RNA and viral load:

I- RNA extraction: HCV viral RNA was extracted from serum samples using fully automated QIAcube instrument and using specific kits; QIAgen columns (QIAamp Viral RNA Mini kit plus QIAmp Viral RNA Mini Accessory SET, cat. No. 1048147 QIagen Inc.) according to the manufacturer' instructions.

II- Real time quantitative PCR: HCV viral load was quantified by using specific TaqMAn® probe-based technology (QIAamp Viral RNA Mini Kit cat. No. 52904 Qiagen Inc.) and 7500 Fast Real Time-PCR system (Applied Biosystems, CA, USA), according to the manufacturer' instructions. The reaction mixture was used in a total volume of 25 including 10 of the sample extract and 15 of the Master Mix which prepared by: 6 Hep. C virus Master A and 9 Hep. C virus Master B. The real-time cycler conditions were performed according to the following conditions: Incubation at 50ºC for 30min then at 95ºC for 15min. to activate theTaq enzyme followed by 50 amplification cycles. Each cycle consists of denaturation at 95ºC for 30sec., primer annealing at 50ºC for 60sec. and primer extension at 72ºC for 30sec.

The patients were placed into three groups according to serum HCV RNA level, estimated by Polymerase chain reaction (PCR):

A- Undetectable: <34 IU/ml.

B- Low viremia: 34-100,000IU/ml.

C- High viremia: >100,000IU/ml.

Statistical analysis:

The statistical analysis was performed using SPSS version 20. Descriptive statistics were employed to investigate general characteristics of the patients. Pearson's correlation to find the correlation between the variables with continuous data and the functional outcome. Student's *t*-test and ANOVA with post-hoc tests were performed to explore the impact of viral load on stroke severity and outcome, as measured by SSS and modified Rankin scale (m-RS) respectively. All the predictive variables were first examined by logistic regression analysis. The analysis was performed by "enter method" among selection methods of variables. Odds Ratio (OR) and 95% Confidence Interval (95% CI) were also determined. p-value <0.05 was considered significant.

Results

A total of sixty (out of two hundred and ten) patients with first ever acute ischemic stroke were included in the study comprising 33 (55%) males and 27 (45%) females. The age of the patients ranged from 45-85 years with a mean of 60 ±9.1 years old (Table 1).

Table (1): Patients characteristics.

Variable	Number	Percentage
Age:		
Mean ± SD	60±9.1	
Sex:		
Male	33	55%
Female	27	45%
Smoking:		
Never smoking	35	58.3%
Current smoker	14	23.3%
Former smoker	11	18.3%
Hypertension:		
Hypertensive	37	61.7%
DM:		
Diabetes type I	10	16.7%
Diabetes, type II	16	26.7%
Cardiac disease:		
RHD	2	3.3%
IHD	21	35.0%
Arrhythmia	3	5.0%
DCM	1	1.7%
Consciousness measured by GCS:		
Mild (13-15)	23	38.3
Moderate (9-12)	25	41.7
Sever (<=8)	12	20.
Stroke severity by SSS:		
Mild (43-58)	10	16.7%
Moderate (26-42)	33	55%
Severe (0-25)	17	28.3%
Anti-HCV Antibodies:		
Negative	19	31.7%
Positive	41	68.3%
HCV RNA viral load (viremia):		
<34 undetectable level	19	31.7%
34-100000 low viremia	16	26.7%
>100000 high viremia	25	41.7%
Outcome:		
Favorable outcome (mRS <3)	21	35%
Unfavorable outcome (mRS ≥3)	39	65%
Mortality:		
Alive	42	70%
Death	18	30%

DM : Diabetes Mellitus.
RHD : Rheumatic Heart Disease.
IHD : Ischemic Heart Disease.
DCM : Dilated Cardiomyopathy.
GCS : Glasgow Coma Scale.
SSS : Scandinavian Stroke Scale.

The overall outcome was favorable (good) in 21 (35%) patients and unfavorable (poor) in 39 (65%) patients. The mean age of those with poor outcome (62±9.7 years) was significantly higher than those with favorable outcome (56.3 ±6.8 years) (p=0.02). The mean HCV RNA viral load was (1, 446, 861.6±2, 341, 507.8) in unfavorable outcome group versus (2, 171.4±7157.9) in the favorable outcome group with statistical significant results (p=0.007) (Table 2).

Table (2): Correlation between patients' demographic and clinical characteristics and functional outcome.

Characteristics	Favorable outcome m-RS <3 (N=21)	Unfavorable outcome m-RS ≥3 (N=21)	p-value
Age in years:			
Mean ± SD	56.3±6.8	62±9.7	0.02
Gender:			
Male	8 (38.1%)	25 (64.1%)	0.05
Female	13 (61.9%)	14 (35.9%)	
Glasgow coma scale:	41.8±12.378	29.45±18.1	0.011
Mildly disturbed (GCS* 13-15)	13 (61.9%)	10 (25.6%)	
Moderate disturbed (GCS 9-12)	5 (23.8%)	20 (51.3%)	
Severely disturbed (GCS <=8)	3 (14.3%)	9 (23.1%)	0.021
Risk factor:			
Smoking:			
Never smoking	14 (66.7%)	21 (53.8%)	0.169
Current smoker	2 (9.5%)	12 (30.8%)	
Former smoker	5 (23.8%)	6 (15.4%)	
Hypertension:			
Hypertensive	8 (38.1%)	29 (74.4%)	0.006
Diabetes mellitus:			
Blood Sugar at admission	163.14±81.797	239.1±147	0.033
Diabetic	4 (19.0%)	23 (59.0%)	0.003
Cardiac disease	10 (47.6%)	17 (43.6%)	0.765
Scandinavian stroke scale:			
Mild (43-58)	2 (9.5%)	8 (20.5%)	0.047
Moderate (26-42)	9 (42.9%)	24 (61.5%)	
Severe (<=25)	10 (47.6%)	7 (17.9%)	
Serology:			
Negative Anti-HCV antibodies	17 (81.0%)	2 (5.1%)	0.002
Positive Anti-HCV antibodies	4 (19.0%)	37 (94.9%)	
HCV RNA viral load measured by PCR:			
<34 undetectable level	17 (81.0%)	2 (5.1%)	0.002
34-100000 low viremia	4 (19.0%)	12 (30.8%)	
>100000 high viremia	0 (0.0%)	25 (64.1%)	
HCV RNA mean ± SD	2,171.4±7157.9	1,446,861.6±2,341,507.8	0.007
Liver function tests:			
Prothrombin time	12.6±1.5	13±1.6	0.360
Prothrombin concentration	85.3±13.1	82.4±13.1	0.429
ALT	24.57±18.1	45.5±34.3	0.011
AST	30.6±21.9	46.7±34.7	0.059
Serum Albumin (man ± SD)	5.12±7.3	3.25±.683	0.118
Lipogram:			
Mean cholesterol	185.52±51.154	194.10±57.076	0.567
Mean triglycerides	151.62±77.539	197.54±105.368	0.085
CBC:			
Platelet	229.4±95.3	227.3±118	0.946
Red blood cells	4.6±0.9	4.6±0.7	0.853
White blood cells	8.8±2.4	9.538±3.7	0.449
Serum creatinine:	0.9±0.4	1.2±1.3	0.284
Erythrocyte sedimentation rate (ESR):			
ESR (first hour)	25.8±19	46.5±25.7	0.002
ESR (Second hour)	51.2±31.4	83.3±35	0.001
Abdominal ultrasound:			
Coarse echo pattern	6 (28.6%)	15 (38.5%)	0.338
Early cirrhotic changes	2 (9.5%)	9 (23.1%)	0.338
Hepatomegaly	0 (0.0%)	3 (7.7%)	0.192
Fatty liver	3 (14.3%)	8 (20.5%)	0.552
Splenomegaly	2 (9.5%)	3 (7.7%)	0.807

Based on multivariate logistic regression analysis, old age and the high level of HCV RNA in stroke patients were an independent predictors of stroke functional outcome and post-stroke mortality after controlling for, hypertension, DM and stroke severity (Tables 3,5).

Thirty percent of study population (18 patients) died; those patients were older, had more stroke severity, more disturbed and higher viremia than those who survived with statistically significantb-differences (Table 4).

Table (3): Predictors of outcome.

	Coefficient (SE)	*P*-value	OR	95% Confidence interval	
				Lower	Upper
Age	0.116	0.047*	1.259	1.003	1.579
Smoking	2.485	0.424	0.137	0.001	17.891
Hypertension	1.539	0.420	3.457	0.169	70.616
Diabetes mellitus	1.885	0.387	5.105	0.127	205.294
Scandinavian stroke scale	0.055	0.255	0.939	0.843	1.046
HCV viral load	0.000	0.049*	1.000	1.000	1.000

Table (4): Three-month mortality.

	Alive	Death	*p*-value
Age	57.67±8.210	65.50±9.109	0.002*
Hypertensive	27 (64.3%)	10 (55.6%)	0.52
Diabetes mellitus	17 (40.5%)	10 (55.6%)	0.282
Scandinavian stroke scale:			
Mild (43-58)	3 (7.1%)	7 (38.9%)	0.009*
Moderate (26-42)	25 (59.5%)	8 (44.4%)	
Severe (<=25)	14 (33.3%)	3 (16.7%)	
Glasgow coma scale:			
Mild (13-15)	21 (50.0%)	2 (11.1%)	0.007*
Moderate (9-12)	16 (38.1%)	9 (50.0%)	
Sever (<=8)	5 (11.9%)	7 (38.9%)	
HCV Viral load:			
Mean ± SD	295,251.6± 743,502.4	2,448,479.7± 3,026,823.3	<0.001 *
<34 undetectable level	13 (31%)	6 (33.3%)	0.005*
34-100000 low viremia	16 (38.1%)	0 (0.0%)	
>100000 high viremia	13 (31.0%)	12 (66.7%)	

Table (5): Predictors of 3-month mortality in patients with acute ischemic stroke.

	Coefficient (SE)	*P*-value	OR	95% Confidence interval	
				Lower	Upper
Constant	2.777	0.009*	0.001		
Age	0.048	0.019*	1.119	1.019	1.229
Hypertension	0.847	0.179	0.321	0.061	1.686
Diabetes mellitus	0.959	0.376	2.335	0.357	15.285
Scandinavian stroke scale	0.033	0.546	0.980	0.918	1.046
HCV viral load	0.000	0.030*	1.000	1.000	1.000

Discussion

Hepatitis C virus infection is a worldwide problem and can lead to hepatic and extra hepatic manifestations including neurological ones **[4, 14-23]**.

Despite its association with insulin resistance, diabetes **[24]** and steatosis **[23]**, the relationship of HCV and stroke remains controversial with lacking of existing studies to accurately determine this relationship.

The present study reported that old age, hypertension, DM, worse consciousness is associated with poor functional outcome and early post stroke mortality, a finding was consistent with other studies **[25,26]**. About two thirds (65%) of our series have unfavorable outcome, while the remaining (35%) has a favorable outcome at the end of the 3 months follow-up.

We found that the HCV RNA level is an independent predictor of poor functional outcome especially with high viremia. This finding was reported also by Lee et al., **[27]** who emphasized the negative prognostic impact of HCV RNA serum levels on outcome and the important role played by HCV. Likewise, Adinolfi et al., **[4]** reported that cerebrovascular acute and chronic events occur in higher prevalence than that observed in the general population in chronic HCV infection. Similarly, many previous studies documented the association between HCV and stroke **[28-30]**. Lastly, there is a meta-analysis concluded for a significantly increased risk of stroke in association with HCV infection **[31]**.

In contrast, Younossi et al., **[32]** negated the effect HCV on stroke. This may be explained by the study populations were not the same terms of such factors as gender, race, and hypertension. In addition to, Völzke et al., **[33]** who reported that HCV infection was found to have no significant impact on stroke, which may be explained by laboratory measurement of only anti HCV antibody and not using HCV RNA level.

The discrepancy in the findings of these previous studies and our study might have resulted from different characteristics of the study population and different prevalence of HCV infection which is relatively high in Egypt.

In this study, we found that high viremia was an independent predictor of post stroke mortality, a finding confirmed by Lee et al., **[27]** who reported that HCV infection is associated with an increased risk of cerebrovascular mortality, particularly for

those with high viremia. Similarly a study carried out on the general United States population reported a significant excess of cardiovascular mortality among anti-HCV positive subjects after considering for conventional risk factors **[34]**. Like other studies **[35,36]** which report chronic HCV infection was associated with an increased mortality from circulatory diseases, this mortality is significantly reduced by interferon and ribavirin treatment **[37]**.

In spite of the Ambiguity of how HCV may predispose to ischemic stroke, carotid plaque destabilization with subsequent rupture and erosion plays a an important role in the development of about one quarter of all cases of ischemic stroke and so, the causal association between chronic HCV infection and atherosclerosis is well documented **[15]**.

Inflammation is a second important mechanism and the key mediator of plaque rupture and thromboembolism **[5,39]**. Infection predispose to atherothrombosis by stimulating the immune responses either locally within vascular tissue by its replication with the carotid plaques or systemically through inflammatory mediators **[6,38,40-44]**. HCV-related vasculitis and predisposition to type 2 diabetes are another mechanism by which HCV lead to stroke **[32,44-47]**.

This study has some restrictions that should be brought into account in evaluating the results. We did not evaluate stroke subtypes in relation HCV infection. Second, we did not follow-up the patients who had interferon treatment to evaluate whether HCV eradication had impacts on cerebrovascular mortality.

In spite of these limitations, the present study has shown that a significant association between serum HCV RNA levels and function outcome of stroke, so HCV infection should be considered as a risk factor of cerebrovascular disease particularly in our locality to decrease its impact on stroke outcome and mortality and should be treated by specific antiviral strategies in order to prevent cerebrovascular disease.

Conclusion:

In conclusion, the present study is among the few studies that exhibit an association between HCV infection, particularly those with high viremia and function outcome of stroke including mortality. So treatment of chronic hepatitis C virus with the new oral antiviral drugs, particularly in Egypt would be helpful to decrease the risk of stroke and its poor functional outcome.

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الحمل الفيروسى للإلتهاب الكبدى المزمن C كمتنبآ بالنتائج قصيرة الآجل للسكتة الدماغية الحادة الآولى

مرض الآوعية الدموية هو عبء صحى كبير للعدوى بفيروس إلتهاب الكبد (سى) دور فى تطور تصلب الشرايين السباتية وترتبط مؤخراً بالنتائج السيئة لدى مرضى السكتة الدماغية. كان الهدف من الدراسة هو إستكشاف القيمة التنبئية للحمل الفيروسى لفيروس إلتهاب الكبد المزمن (سى) على السكتة الدماغية الحادة. وإشتملت الدراسة على ستين مريضاً تم تشخيصهم بالسكتة الدماغية الحادة وتم تقسيم المشاركين فى البحث إلى ٤١ مريضاً لديهم فيروس إلتهاب الكبدى سى و١٩ مريضاً بدون فيروس سى المزمن. تم تقييم شدة السكتة الدماغية وإرتباطها مع الحمل الفيروسى (سى) الذى تم تحديده بواسطة RT-PCR وكانت النتيجة إيجابية فى ٣٥٪ وغير مواتية فى ٦٥٪. تم العثور على مستوى عال من HCV RNA فى دم مرضى السكتة الدماغية ليكون مؤشراً مستقلاً لنتائج السكتة الدماغية بعد تحييد العمرة إرتفاع ضغط الدم ومرض السكرى وشدة السكتة الدماغية. والمرضى الذين ماتوا كان لديهم مستويات آعلى بكثير من HCV RNA مقارنة بالناجين.