A study of some risk factors of ischemic stroke in patients with hepatitis C viral infection

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Abstract: Objectives: The aim was to study the role of Hepatitis C virus (HCV) infection in patients with ischemic stroke. **Methods:** 100 patients with ischemic stroke were evaluated and classified into two groups (group I were patients with ischemic stroke and positive HCV infection & group II were patients with ischemic stroke and negative HCV infection). **Results:** Patients with positive HCV infection were younger [61.72 ± 6vs. 67.42±4.4 years old, respectively; P value <0. 001], had elevated ESR (P value <0. 001), had lower serum levels of total cholesterol and triglycerides (P value <0. 001 and <0. 05, respectively). There was increased incidence of rheumatoid factor, antinuclear antibody (ANA), anticardiolipin antibodies in patients with positive HCV infection (P value <0.001) with higher prevalence of carotid atherosclerosis (P value <0.05).Hypertension was more prevalent in patients with recurrent stroke (p value <0.001). More patients with recurrent stroke had positive ANA, ANCA and anticardiolipin antibodies (P value <0.05). **Conclusions:** HCV infection is a risk factor for earlier and recurrent stroke. Inflammation has a key role.

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1. Introduction:

Stroke is the third leading cause of death worldwide. It is becoming a great health burden in most industrialized countries in future decades. Conventional risk factors for stroke include cardiac diseases, hypertension, diabetes, smoking, alcohol consumption, unhealthy diet, abdominal obesity, lack of exercise, psychosocial stress and depression ***(1)***. Increased evidence indicates that acute and various chronic infectious diseases are important triggers of or risk factors for stroke. However, the association of HCV infection and stroke is not well established.

HCV has infected more than 170 million people worldwide (approximately 3% of the world's population) ***(2)***. In up to 80% of infected patients, HCV established persistent infection, often leading to liver cirrhosis and hepatocellular carcinoma.

Several epidemiological studies have demonstrated that chronic HCV infection is an independent risk factor of stroke or cerebrovascular death ***(3)***. However, Younossi et al., ***(4)*** did not find an association between HCV and stroke.

Analysis of published studies supports the view that HCV infection should be considered a risk factor for the development of carotid atherosclerosis, heart failure and stroke. In contrast, findings from studies addressing coronary artery disease and HCV have yielded conflicting results. Therefore, meta-analytic reviews and prospective studies are warranted ***(5)***.

The aim of this work was to study the role of HCV infection in patients with ischemic stroke.

2. Patients and methods:

This prospective, single center study was conducted at the neurology department of "Benha University hospital" from January 2014 to October 2015. A total of 100 patients with ischemic stroke were evaluated. They were classified into two groups. 50 patients with ischemic stroke and positive for hepatitis C viral infection were classified as group I & 50 patients with ischemic stroke and negative for hepatitis C viral infection were classified as group II.

Consent from the patients and the approval from the ethical committee was obtained.

Patients with hemorrhagic stroke, chronic rheumatologic disease, those who are taking antiviral therapy or interferon within 6 months from admission and patients refusing to participate in the study were excluded.

All patients underwent physical examination, CT brain, ECG, echocardiography, carotid duplex, liver functions, lipid profile, ESR, rheumatoid factor, ANA, ANCA and anticardiolipin antibodies testing.

Statistical analysis

Data were tabulated and statistically analyzed to evaluate the difference between the groups under the study as regard different parameters. Calculations were done using statistical software package namely (SPSS 19) special package for special sciences.

Continuous variables were expressed as means ±SD. Student's t-test was used to compare two groups of unpaired data. Comparisons among patient groups were performed using Pearson chi-square test. Significant variables on univariate analysis were tested in the multivariate logistic regression with the forward stepwise method to identify independent associations with HCV infection.

3. Results

The study sample consisted of 100 patients, 56 patients (56%) were males and 44 patients (44%) were females. their age ranged from 42-75 years with mean age 64.57±5.97 years.

The patients with ischemic stroke and positive for hepatitis C viral infection (group I) were significantly younger than the patients with ischemic stroke and negative for hepatitis C viral infection (group II) with mean age ["61.72 ± 6" years old vs. "67.42±4.4" years old, respectively; P value <0. 001] ***(table 1)***.

No differences were observed between the two groups with regard to the risk factors ***(table 1)***.

Table (1): Baseline data of the patients

Variable	**Group I** (stroke & +ve HCV)	**Group II** (stroke & -ve HCV)	**P value**
Age (Mean ± SD)	61.72 ± 6	67.42±4.4	<0.001
Gender:			
Male	29 (58%)	27 (54%)	>0. 05
Female	21 (42%)	23 (46%)	
Risk factors:			
Diabetes mellitus	16 (32%)	19 (38%)	>0.05
Hypertension	21 (42%)	24 (48%)	>0.05
Smoking	20 (40%)	21 (42%)	>0.05 >0.05
Past history of IHD	14 (28%)	11 (22%)	>0.05
Past history of CVS	7 (14%)	3 (6%)	

There was no significant statistical difference between the 2 groups as regards the presence of atrial fibrillation (AF). None of the patients of the 2 groups had evidence of intracardiac masses or thrombi at the level of transthorathic echocardiography (TTE). There was no significant statistical difference between the 2 groups as regards the LV ejection fraction (EF).

ESR was significantly elevated in patients of group I (50.7 ± 31.3 vs. 24.9 ± 15.4 IU/L, P value <0.001). Patients of group I had significantly lower serum levels of total cholesterol and triglycerides when compared with group II (198. 9 ± 48.9 vs. 246.3 ± 71.7 mg/dl and 187.12 ± 46.5 vs. 227.5± 81.1 mg/dl respectively). There was no significant statistical difference between the 2 groups as regard HDL and LDL levels (P value >0.05) ***(table 2)***.

Table (2): Patients' lipid profile

Group / Parameter	**Group I** (stroke & +ve HCV) **Mean ± SD**	**Group II** (stroke & -ve HCV) **Mean ± SD**	**P value**
ESR	50.7 ± 31.3 IU/L	24.9 ± 15.4 IU/L	<0.001
Cholesterol	198. 9 ± 48.9mg/dl	246.3 ± 71.7mg/dl	<0.001
Triglycerides	187.12 ± 46.5 mg/dl	227.5± 81.1mg/dl	<0.05
HDL	47.1 ± 7.83 mg/dl	45.68 ± 7.15 mg/dl	>0.05
LDL	105.6 ± 17.2mg/dl	110.9 ± 14.5mg/dl	>0.05

There was increased incidence of rheumatoid factor, ANA positivity in patients of group I. Rheumatoid factor was positive in 48% (24/50) of patients of group I and in 12% (6/50) of patients of group II. ANA was found in 8% (4/50) of patients of group I but in none of patients of group II (n = 50). ANCA was positive in 2 patients of group I (4%) but in none of group II patients with no significant statistical difference between the two groups. Anticardiolipin antibodies had significantly increased incidence in group I patients (IgG was positive in 7 patients "14%" of group I and IgM was positive in 5 patients "10%" of group I but in none of group II patients, P value <0.001) ***(figure 1)***.

Based on the results of the univariate analysis which showed the factors associated with HCV related stroke, multivariate regression analysis including these variables significantly associated with HCV-related stroke showed that age (p value 0.002), albumin (p value 0.001), total cholesterol (p value 0.01), ANA (p value 0.04) and aCL IgG (p value 0.04) were factors strictly related with HCV infection.

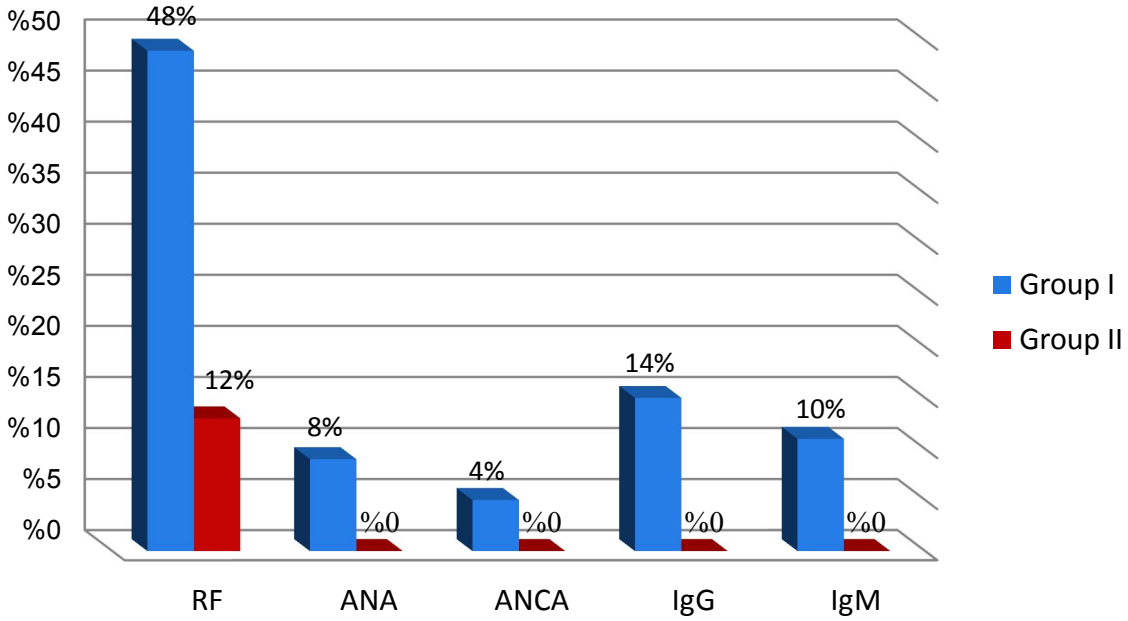

Figure 1: Patients' autoantibodies

There were a significantly higher number of previous cerebral infarctions in patients of group I than those of group II ($P < 0.05$). Patients of group I showed a significantly higher prevalence of carotid atherosclerosis than that observed in the second group (44.44% vs. 14.29%, respectively, $P < 0.05$) ***(figure 2)***.

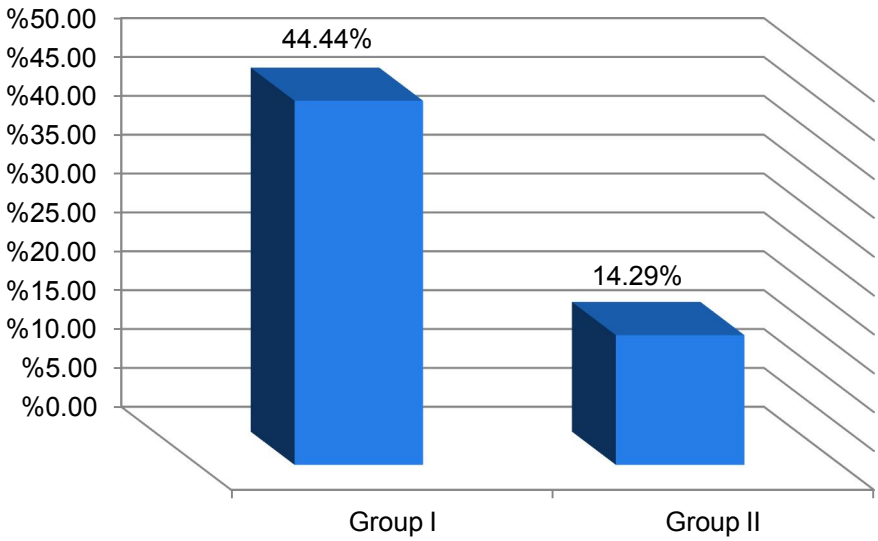

Figure 2: Percentage of patients with carotid atherosclerosis

There was no statistical difference between patients with single or recurrent stroke as regards the age of the patients. No differences were observed between patients with single and recurrent stroke with regard to the risk factors except for hypertension which was more prevalent in patients with recurrent stroke (16 patients "80%" vs. 29 patients "36.25%" respectively, p value <0.001). Systolic and diastolic blood pressures were more elevated in patients with recurrent stroke compared with those who had single stroke (133.5±22.5 vs. 118.6 ± 20.5 mmHg and 84 ±13.5 vs. 76.1 ± 12.2mmHg respectively, p value <0.05) ***(table 3)***.

No differences were observed between patients with single and recurrent stroke as regards heart rate and body mass index. There were more patients with recurrent stroke who had positive ANA, ANCA and anticardiolipin antibodies "IgG and IgM" when compared with those who had single stroke. No differences were observed between patients with single and recurrent stroke as regards the rheumatoid factor ***(table 3)***.

Table (3): Relation between stroke recurrence and the different parameters

Variable	**Single stroke** (n=80)	**Recurrent stroke**(n=20)	**P value**
Age (Mean ± SD)	64.75 ± 5.4	63.85±7.9	>0. 05
Risk factors:			
Diabetes mellitus	28 (35%)	7 (35%)	>0.05
Hypertension	29 (36.25%)	16 (80%)	<0.001
Smoking	33 (41.25%)	8 (40%)	>0.05
Past history of IHD	18 (22.5%)	7 (35%)	>0.05
Clinical examination:			
SBP (mmHg)	118.6 ± 20.5	133.5±22.5	<0.05
DBP (mmHg)	76.1 ± 12.2	84 ±13.5	<0.05
Heart rate (bpm)	80.5± 12.3	85.5± 21.3	>0.05
Autoantibodies:			
Rheumaatoid factor	23 (28.75%)	7 (35%)	>0.05
ANA	1 (1.25%)	3 (15%)	<0.05
ANCA	0 (0%)	2 (10%)	<0.05
aCL (IgG)	3 (3.75%)	4 (20%)	<0.05
aCL (IgM)	2 (2.5%)	3 (15%)	<0.05

4. Discussion:

The study sample consisted of 100 patients with ischemic stroke. 56 patients (56%) were males and 44 patients (44%) were females. their age ranged from 42-75 years with mean age 64.57±5.97 years.

The patients with ischemic stroke and positive for hepatitis C viral infection (group I) were significantly younger than the patients with ischemic stroke and negative for hepatitis C viral infection (group II) with mean age ["61.72 ± 6" years old vs. "67.42±4.4" years old, respectively; *P* value <0. 001].

This is consistent with ***Adinolfi et al., (6)*** who assessed chronic HCV infection as a risk factor of ischemic stroke & found that HCV positive patients were younger in age (p = 0.017) and confirming the recent finding that HCV is a risk factor for an earlier stroke.

In the present study, there was no significant statistical difference between the 2 groups as regarding the sex. Of patients with positive hepatitis C viral infection, 29 patients (58%) were males and 21 patients (42%) were females, while of patients with negative hepatitis C viral infection, 27 patients (54%) were males and 23 patients (46%) were females (*P* value > 0.05)

In the current study, no differences were observed between 2 groups with regard to the risk factors. History of DM was found in 16 patients "32%" of group I vs. 19 patients "38%" of group II. History of HTN was found in 21 patients "42%" of group I vs. 24 patients "48%" of group II. 20 patients "40%"of group I were smokers vs. 21 patients "42%"of group II. 14 patients "28%" of group I had past history of ischemic heart disease vs. 11 patients "22%"of group II. 7 patients "14%" of group I had past history of ischemic stroke vs. 3 patients "6 %" of group II.

These results were in agreement with those reported by ***Adinolfi et al., (6)***. They reported that the prevalence of male gender was lower, although not significant, in HCV positive group. There were no significant differences between HCV positive and negative with respect of smoking (37% vs. 39%), hypertension (50% vs. 59%), diabetes (51.5% vs. 48%) and atrial fibrillation (32% vs. 26%).

In the current study, ECG& echocardiography were done for all the patients to exclude embolic causes of ischemic stroke. There was no significant statistical difference between the 2 groups as regards the presence of AF.

None of the patients of the 2 groups had evidence of intracardiac masses or thrombi at the level of TTE. There was no significant statistical difference between the 2 groups as regards the LV ejection fraction.

In the present study, there was no significant statistical difference between the 2 groups with regard to the routine laboratory values except ESR level. ESR was significantly elevated in patients of group I (P value <0.001).

This is consistent with ***Adinolfi et al., (6)*** who 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(p value = 0.001).

In the present study, patients of group I had significantly lower serum levels of total cholesterol and triglycerides when compared with group II (198. 9 ± 48.9 vs. 246.3 ± 71.7 mg/dl and 187.12 ± 46.5 vs. 227.5± 81.1 mg/dl respectively). There was no significant statistical difference between the 2 groups as regard HDL and LDL levels (P value >0.05).

Similarly, ***Adinolfi et al., (6)*** reported that stroke patients with positive HCV had lower serum levels of cholesterol (p = 0.001) and triglycerides (p = 0.045). Also, ***Butt et al., (8)*** reported that HCV positive patients have lower levels of cholesterol and triglycerides.

There was increased incidence of rheumatoid factor, ANA positivity in patients of group I. Rheumatoid factor was positive in 48% (24/50) of patients of group I and in 12% (6/50) of patients of group II. ANA was found in 8% (4/50) of patients of group I but in none of patients of group II (n = 50). ANCA was positive in 2 patients of group I (4%) but in none of group II patients with no significant statistical difference between the two groups. Anticardiolipin antibodies had significantly increased incidence in group I patients (IgG was positive in 7 patients "14%" of group I and IgM was positive in 5 patients "10%" of group I but in none of group II patients, P value <0.001).

This is in agreement with ***Banks et al., (9)*** who studied serum autoantibodies associated with chronic hepatitis C and found that RF positivity is more prevalent among patients with HCV infection compared to the general population.

Similarly, ***Peng et al., (10)*** who studied the clinical significance of antinuclear antibody in hepatitis C virus infection, reported that antinuclear antibody was present in 11 (23%) of 48 patients with HCV infection. Also, ***Narciso-Schiavon et al., (11)*** who studied antinuclear antibody positivity in patients with chronic hepatitis C, found that 22 patients (9.4%) were positive for ANA. ***Cojocaru et al., (12)*** who studied the prevalence of anti-neutrophil cytoplasmic antibodies in patients with chronic hepatitis C infection, reported a high prevalence of ANCA in the serum of patients with HCV.

However, ***Ordi-Ros et al., (13)*** who studied anticardiolipin antibodies in patients with chronic hepatitis C virus infection, found that only 3% of the patients with chronic HCV infection had aCL (IgG and/or IgM). Other reports have described a frequency of aCL ranging from 3 to 22% ***(14)***. These differences may be due to the methods used in assessment of anticardiolipin antibodies.

In the present study, the findings of the CT/MRI brain showed a significantly higher number of previous cerebral infarctions in patients of group I than those of group II (P < 0.05). 36 patients (72%) of patients of group I had single lesion in CT/MRI while 14 patients (28%) had multiple lesions. 44 patients (88%) of patients of group II had single lesion in CT/MRI while 6 patients (12%) had multiple lesions.

This is consistent with ***Krunoslav et al., (7)*** who assessed the recurrent strokes in patients with chronic hepatitis C infection and found that HCV is a risk factor for stroke recurrence. 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 CHC infection.

In the present study, Patients of group I showed a significantly higher prevalence of carotid atherosclerosis than that observed in the second group (44.44% vs. 14.29%, respectively, P < 0.05).

These results were in agreement with several previous studies evaluating the association between HCV and carotid atherosclerosis. The first study was published in 2002 and showed that HCV infection was associated with increased risk of carotid atherosclerosis ***(15)***.

Also, ***Petta et al., (16)*** evaluated carotid atherosclerosis in biopsy-proven chronic hepatitis C genotype 1 patients and reported that HCV patients had a significantly higher prevalence of atherosclerosis than matched control patients (41.9% vs. 22.9%, respectively).

A large study in Egyptian individuals, including HCV infected patients, HCV subjects with viral clearance, and subjects never infected as controls, showed that the prevalence of carotid atherosclerosis did not vary when patients with active infection were compared to those with past infection. However, HCV infected patients showed a higher risk of

atherosclerosis following adjustment for known cardiovascular risk factors ***(17)***.

Adinolfi et al., (18) assessed carotid atherosclerosis in a large cohort of consecutive liver biopsy-proven chronic hepatitis C patients with and without steatosis. HCV patients showed a significantly higher prevalence of atherosclerosis than that observed in the HCV-negative control group (53.7% vs. 34.3%, respectively, P < 0.0001).

In the current study, based on the results of the univariate analysis which showed the factors associated with HCV related stroke, multivariate regression analysis including the above variables significantly associated with HCV-related stroke showed that age (p value 0.002), albumin (p value 0.001), total cholesterol (p value 0.01), ANA (p value 0.04) and aCL IgG (p value 0.04) were factors strictly related with HCV infection.

Adinolfi et al., (6) used multivariate analysis of the significant variables in univariate analysis. They found that systemic markers of inflammation (Serum CRP, p ¼ 0.0001; serum fibrinogen, p ¼ 0.015; ESR, p ¼ 0.042) and past ischemic heart events (p ¼ 0.03) were factors strictly related with HCV infection.

In the current study, there was no statistical difference between patients with single or recurrent stroke as regards the age of the patients.

These results were in agreement with ***Demirci et al., (19)*** who studied risk factors that affect stroke recurrence and reported that there was no significant difference between first and recurrent stroke groups with regard to the age effect.

No differences were observed between patients with single and recurrent stroke with regard to the risk factors except for hypertension which was more prevalent in patients with recurrent stroke (16 patients "80%" vs. 29 patients "36.25%" respectively, p value <0.001).

These results were in agreement with those reported by ***Demirci et al., (19)***. They found that hypertension was the most frequently encountered and statistically significantly higher risk factor in the first and recurrent strokes in both the first and recurrent strokes.

Also, ***Boysen and Truelsen (20)*** found that stroke recurrence was correlated with hypertension, AF and cigarette smoking in the Chinese population and that controlling these risk factors decreased the recurrence rates considerably.

But, these results were in contrast to those reported by ***Berthet et al., (21)***. They found that diabetes increased the risk of recurrent stroke by 35% principally through an effect on ischemic stroke. This could be explained by the small number of patients in the present study.

Conclusion:

Chronic HCV infection is a risk factor for early and recurrent ischemic stroke independent of the other risk factors as DM and hypertension. Chronic HCV infection is a risk factor for atherosclerosis. Inflammation has a key role in predisposition of ischemic stroke in patients with chronic HCV infection. Hypertension was more prevalent in patients with recurrent stroke. More patients with recurrent stroke had positive ANA, ANCA and anticardiolipin antibodies.

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