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# CHRONIC HEPATITIS B, C, AND STROKE; ASSOCIATION AND PATHOPHYSIOLOGY

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## ABSTRACT

### Background and Objectives:

Hepatitis infection may raise the incidence of stroke and other cerebrovascular abnormalities, according to several studies. However, its association is controversial. This review looked to compile the most recent research on the relationship between HBV and HCV, atherosclerosis, and stroke.

### Methods:

This article reviews the literature on the connection between hepatitis B and C viruses with stroke and atherosclerosis. The search included articles from PubMed, PakMediNet, and Google Scholar, as well as a Medline search using specific keywords and MeSH terms. A total of 2655 articles were identified. Out of these 2655 articles we identified 134 articles in English for review. These 134 articles comprised of original studies, individual case studies, and retrospective cohorts. The review included original research, individual case reports, and retrospective cohorts published after 1990. Studies addressing co-infection with HIV were excluded.

### Results:

After the screening, many articles were selected which included several topics of discussion under the said heading. The studies were closely examined to gather pertinent information relevant to the review's objectives. Most of the literature emphasized the link between chronic hepatitis and the risk of stroke.

### Conclusion:

Although current evidence does tilt the scale in favor of hepatitis-causing cerebrovascular disease, this review study has some limitations, such as the lack of prospective cohorts and limited evidence for the natural history of hepatitis patients in relation to cardiovascular and cerebrovascular diseases.

**Keywords:** HBV, HCV, atherosclerosis, carotid plaque, stroke.

## INTRODUCTION

Leading causes of morbidity and mortality globally are non-communicable illnesses, particularly stroke. Not only is it responsible for one-third of the deaths globally along with significant volumes of physical and mental disabilities, but it is also responsible for an enormous burden on the global economy. In 2008, it was projected that cardiovascular disease and stroke cost the US economy \$297.7 billion in direct and indirect costs.<sup>1</sup> In Pakistan, the prevalence of non-communicable diseases including diabetes, hypertension, and cardiovascular illnesses like stroke is also rising. Conversely, communicable illnesses cause

over half of all fatalities in Pakistan.<sup>2</sup> Among the most common communicable illnesses are hepatitis B and hepatitis C.<sup>2</sup> Stroke has a diverse risk factor profile including non-communicable and communicable diseases such as chronic infections. Fairly modest reforms in the risk factor profile are likely to bring a decline in the overall prevalence of stroke.

## METHODS:

This article summarizes the evidence on the connection between stroke and atherosclerosis and the hepatitis B and hepatitis C viruses. Articles were screened in PubMed, PakMediNet, and Google Scholar by using

keywords such as Hepatitis B virus in Pakistan, the prevalence of HBV in Pakistan, Hepatitis B virus in the general population, epidemiology of HBV in Pakistan, hepatitis C in Pakistan, prevalence of Hepatitis C in Pakistan, hepatitis B and C and stroke, hepatitis B and C and atherosclerosis, hepatitis B and C and carotid intima-media thickness, hepatitis B and C and cerebral venous sinus thrombosis, hepatitis B and C and cerebral hemorrhage; and hepatitis B and C treatment and stroke. Also, a Medline search of the English literature with the MeSH terms (carotid AND atherosclerosis AND hepatitis B, carotid AND atherosclerosis AND hepatitis C) was conducted. A total of 2655 articles were identified. Out of these 2655 articles we identified 134 articles in English for review. These 134 articles comprised original studies, individual case studies, and retrospective cohorts. We also looked through the references of the publications we found to see if there was any further related research that would fit our review. Articles published after 1990 till date were selected to be included in this review. Studies that addressed the co-infection of HBV and HCV with or without HIV were not included.

### **ROLE OF INFECTION IN STROKE**

Ischemic strokes comprise nearly 80% of all strokes worldwide. The atherosclerotic plaques are one of the major contributors to the risk of ischemic stroke. It has been established that carotid atherosclerosis has an independent link with increasing age, male gender, hypertension, greater LDL-C, lower HDL-C, smoking, and diabetes. However, these traditional risk factors contribute to less than half of atherosclerotic/cardiovascular disease risk in developing countries.<sup>3</sup> Kiechl et al. investigated the association between carotid atherosclerosis and the existence of persistent infections of the respiratory system, urinary tract, teeth, and other organs. They demonstrated that, in participants without carotid atherosclerosis at baseline, chronic infections increased the probability of atherosclerosis formation in the arteries (age-/sex-adjusted OR, 4.08 for any chronic infection versus none). Notably, the risk was found to be highest in patients with prominent inflammatory responses.<sup>4</sup> Not only this but the increasing number of infectious pathogens to which an individual has been exposed has been shown to have an independent impact on the progression of carotid atherosclerosis.<sup>5</sup> Nonetheless, the role of chronic infections causing carotid atherosclerosis with subsequent stroke is still controversial and is yet to be explored.

### **POSSIBLE MECHANISM OF STROKE IN INFECTIONS**

The pathogenesis of atherosclerosis is thought to be influenced by bacterial and/or viral infections, either

directly infecting vascular cells or indirectly by inducing cytokines like IL-1, IL-6, and TNF alpha or acute phase proteins like heat shock proteins at non-vascular sites.<sup>6</sup> Apart from this direct effect of infectious agents, some other indirect mechanisms have been highlighted as well. The Bruneck Study's findings showed that smokers' persistent infections may play a role in mediating the pro-atherogenic consequences of smoking cigarettes.<sup>7</sup> Following herpes zoster, VZV vasculopathy is thought to be a risk factor for stroke. VZV can directly infect the intracranial and extracranial arteries during reactivation, which is accompanied by vascular wall destruction, transluminal inflammation, and/or epithelioid macrophages.<sup>8</sup> The peculiar mechanism of infections especially of chronic viral hepatitis in the pathogenesis of atherosclerosis mostly came from in-vitro studies and are still being discovered.

### **THE BURDEN OF CHRONIC HEPATITIS B AND C- GLOBAL VS PAKISTAN**

At least 500,000 people die each year from chronic hepatitis B virus (HBV) infection, which is a global public health problem.<sup>9</sup> Infection with chronic HBV is thought to affect 350–400 million individuals worldwide, with sub-Saharan Africa and Asia-Pacific having the highest rates.<sup>10,11</sup> Hepatitis C virus (HCV) is expected to infect around 170 million individuals globally since its discovery in 1989.<sup>12,13</sup> With a carrier rate of 3–5%, there are an estimated 7–9 million HBV carriers in Pakistan. With the overall prevalence being assessed to be about 2.5–4.3% and 4.8–5.3%, respectively, the mean values of HBsAg and Anti-HCV prevalence are predicted to be 2.6% and 5.3% in the general population.<sup>14–16</sup> In the largest cohort of 47,538 predominantly healthy male individuals, Khokar et al showed that anti-HCV and HBsAg were positive in 5.3% and 2.5% respectively depicting a high seroprevalence as compared to 1.6% in the United States.<sup>17</sup> But the situation was shown to be alarming in the rural Northern population of Pakistan, representing an ethnic group well-known for a high rate of stroke. The overall prevalence of HBV observed in this cohort (n=950) was 21.05% with the majority (78.5%) being male.<sup>18</sup> Furthermore, many patients suffer from co-infections too.

Thus, together with the tremendous incidence of stroke, hepatitis B and C may represent a significant burden of illness in the general population, which is quite concerning for policymakers. Considering these statistics along with the statistics for stroke, it becomes apparent that even the slightest association between the two diseases i.e., chronic viral hepatitis and stroke can have a considerable effect on the prevalence of stroke and the morbidity and mortality associated with it

and eventually the health-related economy.

### **ASSOCIATION OF CHRONIC HEPATITIS WITH ATHEROSCLEROSIS**

The role of chronic hepatitis has been studied in coronary artery disease (CAD). The results have been discordant. According to the findings from a Japanese cohort, individuals with CAD were less likely to have chronic HBV and HCV infections, and these infections were also not linked to the prevalence or severity of CAD.<sup>19</sup> On the other hand, Vasalle et al. demonstrated that HCV seropositivity was a 4.2 odds ratio independent predictor for CAD.<sup>20</sup>

The relationship between chronic infections and atherosclerosis surrogate measures, particularly carotid-intima media thickness (CIMT) and the presence of carotid plaques has received more attention. Evidence suggests that the existence of carotid artery plaque and CIMT is positively associated with seropositivity for HCV. An increased incidence of carotid artery plaque and CIMT was observed to be related to HCV seropositivity in a general health screening of 4784 people, where 104 (2.2%) were HCV positive (adjusted OR 2.85).<sup>21</sup> Ishizaka et al. investigated a potential relationship between HCV core protein positive, a more accurate indicator of ongoing infection than anti-HCV, and carotid atherosclerosis. In the absence of significant liver impairment, HCV core protein positive was revealed to be an independent predictor of carotid plaque (OR 5.61).<sup>22</sup> Fukui et al reported carotid plaque to be more prevalent in diabetic patients with HCV seropositivity than in seronegative subjects.<sup>23</sup> HBV or HCV infection and carotid atherosclerosis were not linked in two more investigations though.<sup>24,25</sup>

Moreover, 15 (0.4%) and 21 (0.5%) of the German adult participants in the research of Health in Pomerania (SHIP), cross-sectional research, respectively, were seropositive for HBsAg and anti-HCV. Anti-HBs and anti-HCV antibody seropositivity were not independently associated with atherosclerotic outcomes such as stroke, CIMT, or carotid plaques.<sup>26</sup> Similarly, research conducted by Ranković I et al. has highlighted the reciprocal relationship between atherosclerosis and HBV, demonstrating how atherosclerosis contributes to the severity of HBV infection in an often-underestimated way. Therefore, it is hypothesized that one of the primary causes of atherosclerosis is HBV-induced inflammation, which in turn impacts how serious the chronic infection disease state is.<sup>27</sup> Riveiro-Barciela et al. and others concluded that individuals with untreated chronic hepatitis B who tested negative for the HBeAg gene had a greater risk of acquiring carotid plaques and atherosclerosis.<sup>28</sup>

Also, Anti-Neutrophil Cytoplasmic Antibody (ANCA), a risk factor for vasculitis and other autoimmune disorders, and autoantibodies might be brought on by the hepatitis C virus (HCV). Mohamed AB et al. found that ANCA levels and HCV antibody levels are correlated, and ANCA-associated vasculitis may increase the risk of ischemic stroke.<sup>29</sup> An HIV-infected patient who has a stroke is more likely to die from an intracranial hemorrhage if they have hepatitis C, which shows that even after the occurrence of a stroke, HCV carries a risk for further anomalies.<sup>30</sup> Solis JG et al conducted a prospective study in which they stated that patients with chronic hepatitis C when given antiviral agents, reduce their risk of atherosclerosis while decreasing the carotid thickness.<sup>31</sup> Adding to this, A review of the currently available literature by Broker et al. stated that patients infected with HCV are at a much higher risk of developing severe coronary artery disease than healthy people, and cardioprotective measures must be taken in treating these patients to reduce the effect of adverse health effects.<sup>32</sup>

Studying the link between HBV infection and intracranial atherosclerotic stenosis (ICAS), researchers discovered a positive connection between the risk of ICAS and the hepatitis B core antibody, pointing to the harmful consequences of HBV.<sup>33</sup> Not only atherosclerosis, but the risk of cerebral aneurysm rupture also increases if a patient has HBV, as stated by Yang Z et al., though the exact mechanism is still unclear.<sup>34</sup> Similarly, the presence of Subclinical Coronary Atherosclerosis in individuals with chronic HCV infection indicates the need for careful evaluations of cardiovascular risk among those affected by HCV.<sup>35</sup>

These findings are imperative to the fact that a clear-cut association exists between chronic hepatitis and the risk for atherosclerosis. However further studies with a larger sample size are needed to warrant a solid association.

### **DIFFERENCES IN THE RISK FACTOR PROFILE IN HCV PATIENTS**

Due to the burden of chronic liver disease and extrahepatic symptoms, such as cardiovascular illnesses, which are linked to increased mortality, hepatitis C virus (HCV) infection is a significant global health concern. The conclusion that HCV infection should be considered a risk factor for the development of carotid atherosclerosis, heart failure, diabetes mellitus, and stroke are supported by analysis of published data.<sup>36</sup> The comorbidities in patients with chronic viral hepatitis have been studied. Butt et al identified 5737 HCV-infected persons receiving dialysis and found that individuals infected with HCV were likely to be young males having comorbidities like

hypertension, co-infection with HBV, and HIV, and were frequently alcoholics and smokers. Contrary to this, they tend to be less likely to have comorbidities like CAD; stroke; peripheral vascular disease; and diabetes. In general, those with HCV infection had higher rates of hypertension and lower rates of CAD and stroke.<sup>37</sup> Wang et al found that type 2 diabetes and HCV infection were only modestly related, with the relationship being highest in early age (age 35 to 49 years) and in liver condition severity as shown by sonographic evidence of fatty liver and chronic liver disease.<sup>38</sup> Further research on the relationship between HCV infection and type 2 diabetes was conducted over seven years in 5000 Taiwanese patients (544, 812, and 116 of whom were seropositive for HBsAg, anti-HCV, and both HBV/HCV, respectively). In patients with HBsAg, anti-HCV, and HBV/HCV coinfection, the cumulative incidence of developing diabetes over the course of 7 years was 7.5%, 14.3%, and 14.7%, respectively, as opposed to 8.6% in subjects who were seronegative. Particularly among anti-HCV seropositive individuals who are younger or have a higher body mass index, HCV infection has emerged as an independent predictor of diabetes.<sup>39</sup> In a cohort of HCV-infected veterans, the odds of being diagnosed with congestive heart failure, diabetes, and hypertension were found to be higher, but lower for CAD and stroke.<sup>40</sup>

Smoking is not only known to increase the risk for cardiovascular diseases but is also shown to influence hepatic enzyme levels. It has been demonstrated that anti-HCV-seropositive individuals who smoke and consume alcohol often have seven times increased likelihood of having elevated ALT levels. To avoid the danger of exacerbating liver impairment, which is a sign of other cardiovascular risk factors including diabetes, patients who are seropositive for anti-HCV should be firmly urged not to smoke or consume alcohol.<sup>41</sup>

Although hypertension, the leading cause of all strokes, was found to be prevalent in HCV-infected individuals, these patients displayed a lower risk of stroke. This is interesting and points toward some other mechanisms which somehow play a protective role because of stroke. This may partly be described by the altered lipid metabolism seen with chronic HCV. Lesser CIMT and plaque after five years in 40 anti-HCV positive subjects seen by Bilora et al provide a suggestion of a protective effect in these seropositive subjects probably because of a reduced lipid synthesis.<sup>42</sup> Moritani et al. determined the seropositivity for HBV and HCV in 1806 subjects and compared it with their serum lipid profile. Adjusted serum lipid levels in the seropositive subjects with HBV and HCV tended to be lower than in the seronegative subjects. The authors found that infection with HBV or

HCV does not influence the severity of arteriosclerosis in healthy subjects.<sup>43</sup> Reduced hepatic cholesterol synthesis and increased LDLr expression with increased LDL clearance have been projected in chronic HCV. In conclusion, this causes hypertriglyceridemia and reduced levels of apoB, LDL-C, HDL-C, and total cholesterol.<sup>44</sup> Furthermore, interferon-alpha is also shown to be associated with a rise in total and VLDL-triglycerides, VLDL-C and apo B, and a fall of HDL-cholesterol and apo A1.<sup>45</sup> The resultant change in the lipid profile with reduced protective cholesterol (HDL-C) and increased harmful cholesterol (mainly LDL-C) favors a negative association with cerebrovascular diseases. The development of atherosclerosis and stroke may also be influenced by a few additional factors. Given the presence of different antibodies, particularly in chronic HCV-infected individuals with concurrent stroke, this may also include autoimmune processes.<sup>46</sup>

Bayraktar et al. compared the association of HCV seropositivity and autoimmune hepatitis with the presence of autoimmune antibodies like antinuclear antibodies (ANA). In 162 chronic HCV subjects, ANA positivity was seen in 63% of similar subjects with autoimmune hepatitis. The rate of SMA positivity WAS also found to be 65% in chronic HCV infection.<sup>47</sup>

This supports the argument that HCV leads to atherosclerosis through a multifactorial mechanism. Atherosclerosis may then lead to the causation of cerebrovascular diseases i.e., stroke.

#### **ASSOCIATION OF CHRONIC HEPATITIS WITH TRADITIONAL CARDIOVASCULAR RISK FACTORS**

As stated by Babikar A, the available data provide evidence that Chronic hepatitis infection raises the likelihood of both hidden and probable symptomatic cardiovascular disease (CVD). This occurs through a complex series of events involving various factors, such as immune and inflammatory impacts, disturbances in metabolism, and potentially the direct influence of the HCV virus on the heart.<sup>48</sup> Furthermore, a study conducted by Iorga RA summarized that, apart from causing changes in the liver, chronic HCV infection has several impacts on the entire body, which are closely linked to conventional risk factors for cardiovascular disease. These effects have given rise to the idea that chronic HCV infection could be regarded as a risk factor for cardiovascular problems.<sup>49</sup> In a 17-year follow-up of 22,472 participants in a community-based trial, 3931 of whom were HBV seropositive, HBsAg positivity was not linked to an elevated risk of death from atherosclerosis-related or cardiovascular illnesses.<sup>50</sup> The prevalence of high cardiovascular-risk



atherosclerosis and the carotid intima-media thickness were both significantly higher in the hepatitis C-infected group compared to the control group, indicating that chronic hepatitis C was linked to a high risk of carotid atherosclerosis.<sup>[51]</sup>

The link between lipid markers and hepatitis was also established in two studies. Muñoz-Cabrejas et al. stated HCV infection was shown to be positively correlated with the development of atherosclerosis and cardiovascular illnesses, even though total cholesterol and lipid fractions were lowered in individuals with chronic HCV infection.<sup>52</sup> Alternatively, the treatment of patients with HCV had no impact on the atherosclerosis markers but was evident with a rise in serum LDL.<sup>53</sup> To determine the overall prevalence of atherosclerotic cardiovascular disease in persons with hepatitis C virus infection, a systematic review and meta-analysis were also carried out. According to this study, HCV is a significant risk factor for atherosclerosis and cardiovascular disease, with lower- and middle-income nations enduring the most of this burden.<sup>54</sup>

#### **ASSOCIATION OF STROKE WITH CHRONIC HEPATITIS AND ALTERED LIVER ENZYMES**

Only about 7 percent of total body cholesterol circulates in plasma, mostly in the form of LDL-C, which predisposes to atherosclerosis.<sup>55</sup> Multiple large randomized controlled trials have established the role of statins (HMG-CoA reductase inhibitors) in hyperlipidemia and the prevention of atherosclerosis and major cardiovascular events including ischemic stroke. The safety of statins, especially the potential to cause hepatotoxicity (the so-called transaminitis) is a concern. No discernible difference in the occurrence of increases in liver enzyme levels with statin therapy was detected in participants with or without HCV infection, despite the HCV veterans having higher baseline liver enzyme levels. On the other hand, the HCV-infected population that was not receiving statin treatment was more likely to see significant transaminase level rises. These findings imply that statin medication may be safely provided without a significant risk of hepatotoxicity and that there is not a larger risk of changes in liver biochemistry values in individuals with HCV infection.<sup>56,57</sup>

According to estimates, statin medication is a secure choice for treating dyslipidemia in people with nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and HCV infection which allows for a subsequent normalization in liver enzymes.<sup>58</sup>

#### **ASSOCIATION OF STROKE WITH CHRONIC HEPATITIS, WITH AND WITHOUT LIVER FIBROSIS**

In the study by Petta et al., 73 (41.9%) genotype 1 chronic HCV patients and 40 (22.9%) controls both had carotid plaques. Patients over 55 were found to have a comparable frequency of carotid plaques whether they had severe fibrosis or not. Also, it was discovered that patients under 55 with severe hepatic fibrosis had a higher risk of developing early carotid atherosclerosis.<sup>59</sup> In the study by Wang et al., it was seen in 1.9%, 10.2%, and 5.2% among HBsAg-positive, anti-HCV-positive, and coinfecting subjects, respectively, compared to 1.3% in the seronegative subjects. Also, the prevalence of thrombocytopenia among anti-HCV-positive subjects was observed to increase with the severity of liver disease, while in HBsAg-positive subjects, this happened in the presence of advanced liver disease only. Therefore, HCV infection was shown to have a strong association with thrombocytopenia, which was correlated with the extent of hepatocellular damage and hepatic fibrosis.<sup>60</sup>

#### **ASSOCIATION OF CHRONIC HEPATITIS WITH STROKE MORTALITY AND LONG-TERM OUTCOME**

The blood HCV RNA level and HCV genotype of persons who tested positive for anti-HCV were examined in another sizable community-based prospective cohort trial that included 23,665 participants. According to estimates, the cumulative risk of cerebrovascular deaths was 1.0% and 2.7% for anti-HCV seronegative and seropositive individuals, respectively. A multivariate-adjusted hazard ratio for cerebrovascular death was 2.18 and 2.82 for individuals with high serum levels of HCV RNA and anti-HCV seropositive antibodies, respectively. There was no discernible link between HCV genotype and cerebral vascular death. Consequently, chronic HCV infection served as a separate risk factor for cerebrovascular deaths, with a biological gradient of cerebrovascular mortality with increasing serum HCV RNA levels.<sup>61</sup> The available literature on the study conducted by Adinolfi L E appears to align with the notion that chronic HCV infection contributes to the risk of atherosclerosis, the onset of cardiovascular diseases, and notable cardiovascular mortality therefore, it seems feasible to suggest non-invasive screening for atherosclerosis in all individuals with chronic HCV infection.<sup>36</sup> Additionally, it has been demonstrated that stroke in HCV-infected individuals receiving dialysis is linked to a higher risk of fatality.<sup>62</sup>

#### **HBV AND HCV PLATELET COUNT AND MEAN PLATELET VOLUME**

By interacting with the endothelium and leukocytes or

by secreting pro-inflammatory mediators, platelets provide a crucial connection between inflammation, thrombosis, and atherogenesis. The prevalence of thrombocytopenia in chronic viral hepatitis has been established for a long time. Though different studies used different definitions of thrombocytopenia and had heterogeneity in their study design, its prevalence was found to range from 0.16% to 45.4%, mostly up to 24% or more.<sup>63</sup> In the study by Wang et al., it was seen in 1.9%, 10.2%, and 5.2% among HBsAg-positive, anti-HCV-positive, and coinfecting subjects, respectively, compared to 1.3% in the seronegative subjects. Also, the prevalence of thrombocytopenia among anti-HCV-positive subjects was observed to increase with the severity of liver disease, while in HBsAg-positive subjects, this happened in the presence of advanced liver disease only. Therefore, HCV infection was shown to have a strong association with thrombocytopenia, which was correlated with the extent of hepatocellular damage and hepatic fibrosis.<sup>64</sup>

A measure of platelet size called mean platelet volume (MPV), which has also been suggested as a sign of platelet activation is used. Large platelets have more dense granules, create more thromboxane A<sub>2</sub>, and aggregate more readily *in vitro* in response to ADP and collagen, making it a measure of platelet activity.<sup>65</sup> It has been documented in individuals with vascular risk factors and diseases, including acute stroke, with fluctuation in the levels depending on the kind, severity, and duration of stroke.<sup>66,67</sup>

Additionally, it has been demonstrated that when MPV was higher than 11.25 fl (OR 2.9), there was a significant correlation between it and the degree of carotid stenosis in patients with atherothrombotic stroke. In individuals who have had an atherothrombotic stroke, a high MPV may thus be used as a measure of the degree of carotid stenosis.<sup>68</sup> Elevated MPV is also shown to serve as a predictor for venous thromboembolism.<sup>69</sup> It is linked to acute myocardial infarction, mortality after myocardial infarction, and restenosis after coronary angioplasty.<sup>70</sup> However, the MPV assessed during acute stroke is reported to have controversial associations with the outcome after acute ischemic stroke.<sup>71,72</sup> Similarly, in a population-based survey, Biino et al. failed to determine whether the elevated MPV in the presence of acute thrombosis represents a complication or a contributor to thrombosis.

Not much data is available on the association of MPV in patients having chronic HCV and acute stroke. Nevertheless, Turhan et al. showed that, based on MPV, their inactive HBsAg carriers tended to have increased

platelet activation and thus carry a high atherothrombotic risk.<sup>74</sup> Ntaios et al. showed that the platelet count and history of hypertension were the only factors that determined MPV in 636 individuals who had an acute ischemic stroke.<sup>75</sup> Interestingly, both factors are often met and known to have important implications in chronic viral hepatitis, especially HCV. The exact relationship between the two diseases is still not defined. However, the involvement of platelets in the pathogenesis of stroke appears to be varied pathogenesis of stroke, however, appears to be varied considering the findings proving a disparity in the platelet behavior in chronic viral hepatitis, thrombocytopenia on one side, and a predisposition to have an increased MPV on the other side.

### **HEPATITIS B AND STROKE**

On the potential connection between HBsAg seropositivity and atherosclerosis, conflicting results have been published. Moreover, few data are available about the relationship of HBV in the causation of stroke. The correlation of HBsAg seropositivity with stroke and myocardial infarction in a cohort of young Korean men (n=521,421) appeared to be related to the liver damage brought on by HBV infection. Through causing a pro-inflammatory effect, HBsAg seropositivity did not seem to be a significant factor in atherothrombosis.<sup>76</sup> However, it has also been seen in individuals with healthy liver functioning. Kim et al described a young man with reactivated HBV who suffered a transient ischemic attack and was found to have a diffuse intracranial and extracranial atherosclerotic disease with stenosis involving multiple large cerebral arteries even in the absence of traditional risk factors.<sup>77</sup>

Contrary to this non-inflammatory phenomenon, Etgen et al described a middle age HBV patient of Asian descent who suffered an ischemic stroke secondary to different degrees of stenosis involving the common carotid and subclavian arteries secondary to Takayasu's arteritis.<sup>78</sup> These cases propose a diverse mechanism of stroke in HBV subjects. Whether this is by chance or is secondary to HBV infection needs to be delineated in future studies.

### **HEPATITIS C AND STROKE**

There are various extrahepatic symptoms usually associated with hepatitis C virus infection. Among the neurological complications, the most often reported complication is sensorimotor polyneuropathy followed by transverse myelopathy and cognitive impairment chiefly associated with the presence of mixed cryoglobulinemia (MC). Stroke has been seldom reported in chronic viral hepatitis but when reported, it has mostly been related to MC and vasculitis.<sup>79</sup>

## **HCV AND CRYOGLOBULINEMIA**

Much of the data on HCV-associated extrahepatic manifestations point towards a strong association with MC. Similar is true for stroke. Most stroke cases reported in HCV patients have been demonstrated to be connected to MC. Cell-mediated autoimmunity leading to vascular injury through an unidentified antigen has been suspected in its pathogenesis. The first report in this regard was published by Petty et al who described two young women with cerebral ischemia, HCV, and MC. One had evidence of narrowing of the large intracranial arteries along with MC and positive rheumatoid factor.<sup>80</sup>

Soon after that, Dawson et al reported two HCV seropositive patients who suffered an ischemic stroke; one with documented granulomatous angiitis and the other with MC, multiple areas of focal narrowing in the cerebral arterial circulation, and suspected cerebral vasculitis. Warfarin, cyclophosphamide, and corticosteroids helped the patients recover completely.<sup>81</sup> Similarly, another chronic HCV patient who developed a lacunar cerebral infarction was found to have high titers of anticardiolipin antibodies (ACA). Following IFN therapy, HCV RNA, as well as ACA, became undetectable and there were no further thromboembolic events during the follow-up.<sup>82</sup>

However, HCV infection and recurrent large artery ischemic stroke have also been described in the presence of normal intracranial and extracranial cerebral arteries, along with concomitant MC associated with cryoglobulinemic glomerulonephritis and secondary arterial hypertension.<sup>83</sup>

## **TREATMENT OF HCV AND THE LIKELIHOOD OF A REDUCTION IN RISK OF STROKE**

Direct-acting antiviral (DAA) drugs such as Sofosbuvir are a prospective treatment for chronic HCV infection because it has several benefits over currently available treatments, including the ability to treat patients with decompensated liver disease and those who cannot take treatments containing interferon and these patients are shown to have a less risk of stroke.<sup>84,85</sup>

## **INTERFERON (IFN) AND STROKE**

A well-known side effect of IFN treatment is bone marrow suppression which results in cytopenia.<sup>86</sup> Theoretically, cytopenia as thrombocytopenia puts these patients at increased risk of bleeding complications, including intracerebral hemorrhage. Although patients with chronic HCV infection often experience mild cytopenia, severe cytopenia is uncommonly reported and is typically brought on by IFN alpha therapy.<sup>87</sup> Elderly chronic HCV patients are more likely than younger individuals to experience cytopenia while

undergoing therapy.<sup>88</sup> Few cases have been described describing the occurrence of intracerebral hemorrhage concerning IFN therapy. Ferencz et al. have reported three episodes of intracerebral hemorrhage in a population of 1460 HCV-infected patients and suggested the possibility of a link between HCV and its treatment and the occurrence of this serious complication.<sup>89</sup> Nishiofuku et al. also described a middle age ex-smoker man with no comorbid or cytopenia who developed putaminal hematoma during treatment with pegylated-IFN $\alpha$ -2b while serum HCV-RNA was undetectable.<sup>90</sup>

These tenuous reports certainly suggest a potential link between IFN treatment and intracerebral hemorrhage.

## **HEPATITIS AND CEREBRAL VENOUS SINUS THROMBOSIS (CVST)**

Literature reveals only two cases of cerebral venous sinus thrombosis which have been described in association with chronic viral hepatitis. One was described as a 19-year-old HBV seropositive man with Evans syndrome and a prothrombin gene mutation who was taking lamivudine for chronic HBV.<sup>91</sup> The other one was a 44-year-old HCV seropositive alcoholic male with liver cirrhosis and concomitant deficiency of protein C, protein S, and antithrombin III.<sup>92</sup> However, whether this relationship was by chance, or it was only secondary to concomitant thrombophilia could not be clearly defined.

## **HEPATITIS AND INTRACEREBRAL HEMORRHAGE (ICH)**

Spontaneous ICH has been defined in connection with the IFN therapy in hepatitis subjects as noted above. Despite the thrombocytopenia that is often encountered in chronic viral hepatitis, no definite relationship has been defined yet between the two entities to date. Symptomatic ICH is a known and most-frightening complication of thrombolytic therapy. As thrombolytic (tPA) administration is contraindicated if the platelet count is below 100/L, it is challenging to decide the role of platelets in symptomatic ICH. But none of the major risk factors for clinically significant ICH (older age, clinical stroke severity at admission, uncontrolled blood pressure, hyperglycemia, early changes on a CT scan, large baseline diffusion lesion volume, and leukoaraiosis on an MRI) is linked to chronic viral hepatitis.<sup>93</sup>

## **TREATMENT OF ISCHEMIC STROKE IN CHRONIC VIRAL HEPATITIS**

Acetylsalicylic acid, also known as aspirin or ASA, is a crucial part of the treatment of ischemic stroke victims. In a few limited trials, it has been investigated to decide its function in chronic viral hepatitis. In a cell culture



system, Trujillo et al. investigated the impact of ASA on viral replication and protein expression. 58% of HCV-RNA and protein levels were found to be suppressed by ASA. These data imply that ASA could work well as an adjuvant in the treatment of chronic HCV infection.<sup>94</sup> This finding may be important as it is proven that treating chronic viral hepatitis leads to a reduction in the associated vascular risk including atherosclerosis. This in-vitro trial, however, is insufficient to decide the safety and effectiveness of ASA in chronic viral hepatitis individuals who have or are at risk for ischemic stroke. Additionally, supplementing with curantyl has been suggested to help individuals at risk for thrombotic problems achieve a more quick and more profound normalization of platelet activity.<sup>95</sup> But its utility in clinical practice, especially in chronic viral hepatitis needs to be verified in large clinical trials.

Furthermore, mechanical thrombectomy emerges as a safe and effective approach for treating individuals with acute ischemic stroke, exhibiting favorable outcomes when contrasted with conventional medical treatment alone.<sup>96</sup> Similarly, Thrombolysis plays a prominent role in the contemporary management of acute ischemic stroke (AIS), supported by compelling evidence showcasing its effectiveness when administered within 4.5 hours of the onset of symptoms.<sup>97</sup>

Only about seven percent of total body cholesterol circulates in plasma, mostly in the form of LDL-C, which predisposes to atherosclerosis.<sup>95</sup> Multiple large randomized controlled trials have established the role of statins (HMG-CoA reductase inhibitors) in hyperlipidemia and the prevention of atherosclerosis and major cardiovascular events including ischemic stroke. The safety of statins, especially the potential to cause hepatotoxicity (the so-called transaminitis) is a concern. No discernible difference in the occurrence of increases in liver enzyme levels with statin therapy was detected in participants with or without HCV infection, despite the HCV veterans having higher baseline liver enzyme levels. On the other hand, the HCV-infected population that was not receiving statin treatment was more likely to see significant transaminase level rises. These findings imply that statin medication may be safely provided without a significant risk of hepatotoxicity and that there is not a larger risk of changes in liver biochemistry values in individuals with HCV infection.<sup>98,99</sup> According to estimates, statin medication is a secure choice for treating dyslipidemia in people with nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and HCV infection.<sup>100</sup>

Additionally, given their potential elevated risk of cardiovascular diseases, such as stroke, the recent

description of an HCV-associated dysmetabolic syndrome (a triad of insulin resistance, hypocholesterolemia, and steatosis) suggests that these patients may need statin therapy.<sup>101</sup> Statins, like ASA, have been hypothesized to function as an adjuvant treatment for HBV or HCV infection because of their impact on LDL receptors, which are thought to be the HCV's presumed point of entry into hepatocytes. Since HCV RNA replication occurs on lipid rafts, the statins' inhibition of cholesterol synthesis, particularly Fluvastatin, may prevent HCV replication. Additionally, transaminitis is reported to heal spontaneously usually (70%) without the need for treatment withdrawal, which is likely the consequence of drug tolerance or adaptation.<sup>102,103</sup> It is noteworthy that there is also data that statin therapy is associated with an up-regulation in LDL receptors, as the liver is thought to respond to cholesterol deprivation by up-regulation of LDL receptors, and thereby an increased chance of virus to entering hepatocytes via interactions with LDL receptors.<sup>104</sup> Statins thus may enable HCV infection which may counterbalance the antiviral effects observed in vitro and worsen the possible relationship of HCV with atherosclerosis.<sup>104</sup>

Whatever the effect of statin on HCV replication and viral load may be, it sounds evident however, that statin use is safe in chronic viral hepatitis and can be started safely when needed.

### **SUMMARY LINKING STROKE WITH CHRONIC HEPATITIS INFECTION, ELEVATED LIVER ENZYMES, AND PRESENCE OF FIBROSIS**

It is evident from the above-mentioned points that chronic hepatitis infection, as well as other factors such as elevated liver enzymes, viral load, presence or absence of fibrosis, and traditional cardiovascular risk factors, tend to impact the risk of stroke. Chronic hepatitis B infection has been shown to have a conflicting relationship with stroke, as only some articles show a positive correlation, while others don't seem to have a link between these two modalities at all. Moreover, patients having elevated liver enzymes who were not treated with statins were found to have a greater risk of major cardiovascular events including ischemic stroke. Liver fibrosis occurrence also tends to increase the risk of stroke and carotid plaques. However, studies with larger sample sizes are needed to warrant a proper correlation among the above-mentioned modalities.

### **LIMITATIONS AND FUTURE DIRECTIONS**

There are also limitations to this review study. Most of the studies included are non-prospective cohorts which

reduces the level of evidence. Furthermore, there is limited evidence for the natural history of hepatitis patients for cardiovascular or cerebrovascular diseases, most majorly including stroke. Most of the drug trials, e.g., IFN for reducing the severity of hepatitis, have limited focus on the cardiovascular outcomes of the patient. Additionally, certain lab markers, including, but not limited to, viral DNA/RNA and autoimmune antibodies, and thrombophilia, were not checked in all the patients which can be a confounding factor. There was also no data on brain biopsy in cases of stroke caused by HCV. Different studies used a wide spectrum of contrasting cut-off values for lab tests like mean platelet volume and platelet count, which further adds

to the weakness of the study. There was also no choice of seropositivity markers like anti-HBs. Moreover, subjects with elevated liver enzyme levels or chronic liver disease were excluded from most clinical trials. There are many future directions for further research on the said topic. A detailed mechanism of how viral hepatitis can lead to stroke must be explored, and a treatment plan must also be devised for it. Thrombolytic therapy for hepatitis patients must also be explored. Lastly, the role of antiplatelets and their relationship with the histology and serum markers of viral progression of hepatitis should also be researched upon using clinical trials.

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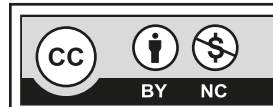
Authors' contribution:

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**Adnan Yousuf;** Concept, design, data collection, data interpretation, manuscript writing

**Mohammad Wasay;** Data interpretation, manuscript review

All the authors approve the final version to be published and agree to be accountable for all aspects of the work.



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