Non-alcoholic fatty liver disease in cerebrovascular disease: a bystander or a real risk factor?

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Over the past decade, non-alcoholic fatty liver disease (NAFLD) has emerged to become one of the most common causes of decompensated cirrhosis, and the leading primary liver disease etiology for liver transplantation. Although NAFLD is a well-established risk factor for cardiovascular disease, its association with cerebrovascular disease is less conclusive. Furthermore, the risk factors that are associated with the development of NAFLD, including obesity, diabetes mellitus, hyperlipidemia, and hypertension, are similar to those that increase the risk of cerebrovascular events. Although the association between NAFLD and cerebrovascular events has been reported, whether NAFLD is a true independent risk factor for strokes or a mere consequence of the shared metabolic risk factors remains to be determined.

In a meta-analysis of nine studies, NAFLD increased the risk of strokes (OR = 2.32, 95% CI 1.84–2.93, $p < 0.001$), and the effect was observed in both Caucasians and Asians [1]. However, in a recent study of over 120,000 adults with a diagnosis of NAFLD/NASH, after adjusting for cardiovascular risk factors, NAFLD was not found to be associated with an increased stroke risk [2]. There may be many factors accounting for the discrepancies in results in these cohort studies [3–7]. Selection bias is unavoidable, and those NAFLD patients included in specialist referral centres may have more risk variables than those in the primary care settings, and may undergo significant lifestyle changes after being diagnosed. Important data may not be captured, such as incidental NAFLD cases during follow-up for control

groups, medication usage including anti-diabetic and anti-lipid drugs, and physical activity. The longer duration of follow-up that is needed to assess stroke endpoints may lead to large numbers being lost to follow-up, low number of patients with endpoints, with increase in type 2 error. The different modalities used to diagnose NAFLD between studies will also limit the comparability between these studies. Therefore, the extent to which NAFLD increases the risk of stroke remains debatable. Furthermore, it is possible that non-alcoholic steatohepatitis (NASH) rather than bland steatosis, and the presence of liver fibrosis, both of which are not detected on imaging, increases the risk of stroke [8].

The mechanistic effect whereby NAFLD increases the risk of stroke remains unclear, although current evidence suggests that it is underpinned by a chronic inflammatory state. This may create a prothrombotic tendency with increase in platelet activity and endothelial dysfunction. Up-regulation of pro-atherogenic transcription factors may also lead to the development of atherosclerotic lesions. Indeed, higher carotid arterial stiffness and increase in arterial wall thickness and thickness of the intima-media index of the internal carotid artery has been associated with NAFLD, which may increase the risk of subsequent stroke events [9, 10]. Furthermore, vascular damage may occur with oxidative stress due to the production of reactive oxygen species as a result of mitochondrial dysfunction. Apart from increase in platelet activity, NAFLD may also be associated with increase in tissue plasminogen activator-1 inhibitor and factor VIII, IX, XI, and XII activities, and a reduction in Protein C, thereby further increasing the prothrombotic imbalance [11, 12]. Finally, NAFLD may also contribute to the unfavourable lipid profile that may heighten the risk of stroke and self-perpetuate the hepatic fat deposition. NAFLD has been associated with the atherogenic dyslipidemia phenotype, secondary to the overproduction of larger triglyceride-rich very low-density lipoprotein (VLDL) particles from the liver [13]. The effects of increase lipid synthesis together

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with underlying insulin resistance may result in a higher triglyceride and lower HDL-cholesterol level.

The retrospective cross-sectional study conducted by Mori et al. in the current issue evaluated the frequency of NAFLD and the risk factors associated with the development of NAFLD in 676 acute stroke patients aged 40–79 years. Using ultrasound, 267 (39.5%) of patients had NAFLD, which was comparatively higher than the previously reported 26.4% from the general Japanese population. In general, the prevalence of NAFLD in patients experiencing cerebrovascular events is quite variable, ranging from 8 to 44% [14]. When compared to those without NAFLD in the current study, patients with NAFLD were younger, had higher levels of liver enzymes, serum albumin, HbA1C, serum lipids (excluding LDL-cholesterol), blood pressure, and anthropometric values, and lower AST/ALT ratio. In addition, higher levels of lauric acid, myristic acid, palmitic acid (PA), stearic acid, oleic acid, linoleic acid, dihomo- γ -linolenic acid (DGLA), arachidonic acid (AA), α -linolenic acid, and docosahexaenoic acid (DHA) were observed in patients with NAFLD, whereas no difference was found in eicosapentanoic acid.

After multivariate analysis, high BMI, low AST/ALT ratio, high albumin, PA% and DGLA levels were independently associated with NAFLD in acute stroke patients. In contrast, other well-known risk factors including blood pressure, glucose level, HbA1C level, total cholesterol and triglycerides were not independent factors. A high BMI is not surprising and is a well-established risk factor. Similarly, there is data showing a positive correlation between ALT/AST ratio with NAFLD risk and hepatic fat infiltration. A higher ALT may indicate underlying inflammatory activity, and chronic inflammation may induce insulin resistance and steatosis in the liver. The finding of a high albumin as an independent risk factor is unexpected, and somewhat paradoxical, as a lower albumin would be anticipated, especially for those with advanced liver disease. In the early stages of liver disease, it would be unusual for any significant differences between NAFLD and non-NAFLD patients. Unfortunately, the authors do not offer any potential explanations for this finding. Whether the association of higher albumin with NAFLD is peculiar to acute stroke patients remains to be determined. It is also possible that non-NAFLD patients may have underlying renal dysfunction or other chronic inflammatory disease that was not captured. Finally, this may be due to the limitations of the statistics employed using only variables without multicollinearity as defined by a low variance inflation factor of less than 3.

Despite this, the current study may shed light on the role of different fatty acids on NAFLD in acute stroke patients. The same group has published on the association of serum fatty acids and higher serum DGLA levels with the age of onset of acute ischemic stroke and intracerebral haemorrhage

[15, 16]. DGLA is commonly used as a health supplement for its alleged effects in a variety of diseases, including suppression of chronic inflammation, vasodilation and blood pressure lowering, and inhibition of progression of atherosclerosis [17]. On the other hand, DGLA is metabolized to arachidonic acid, and subsequently into prostaglandin E₂, thromboxane A₂, or leukotriene C₄, thereby potentially increasing the risk of cerebrovascular events by the virtue of a pro-inflammatory state. Therefore, it would appear that the types of fatty acids and their metabolites may determine the quality of the triglyceride, and some in fact may not be detrimental. A previous study has shown that individual serum trans, saturated, and monosaturated fatty acids were positively associated with ischemic stroke, in contrast to individual n3 and n6 polyunsaturated fatty acids where there was an inverse relationship [18]. It would be important to identify why some patients have higher DGLA than the others, and a detailed dietary history would be helpful.

Before we can draw any firm conclusions from the study, there are several aspects to consider. First, the issue with higher serum albumin remains unresolved. Second, as with all cross-sectional studies, reverse causality remains a possibility, and selection bias cannot be eliminated. Thirdly, the diagnosis of NAFLD was based on ultrasound only. Last, and most importantly, a comparison arm consisting of non-stroke patients is lacking, therefore, we cannot ascertain whether the current findings are specific for acute stroke patients, and why one would expect the risk factors to vary in stroke, as compared to other cardiovascular diseases. Furthermore, the lack of a control group means that we cannot determine whether there is any actual association of NAFLD and stroke. Ultimately, acute stroke is the more important endpoint, and a control arm is required to determine if factors associated with NAFLD development are also important in stroke occurrence. Identifying risk factors associated with NAFLD in acute stroke patients in itself has less clinical relevance, especially in the absence of liver sequelae.

There is evidence to suggest that the presence of NAFLD not only can increase the risk of stroke, but also impact on the outcome after a stroke event, although the results have been contradictory. Some studies have shown that NAFLD may be associated with more severe stroke and worse outcome [19]. Paradoxically, another study showed that a higher burden of hepatic steatosis was associated with less severe stroke and better functional outcome [20]. It remains possible that the underlying liver fibrosis and not steatosis is responsible for outcomes after stroke [21]. Indeed, the presence of liver fibrosis has been shown to be associated with unfavourable long-term prognosis in ischemic stroke or transient ischemic attack patients [8, 21].

As the relationships between NAFLD, steatosis, fibrosis, stroke risk, and stroke outcome are complex, well-designed randomized controlled trials with adequate follow-up and

sample size to demonstrate a reduction in incidence of stroke with treatment of NAFLD may be a valuable addition in filling the lacunae in evidence so far. A standardized method for the diagnosis of NAFLD should be adopted and repeated at intervals along with updated histories on medication, physical activity, dietary modification, and the development of metabolic disorders. This will allow identification of risk factors underlying NAFLD and cerebrovascular disease, assessment of their dynamic impact on stroke development, and allowing better management directed at reducing these risks.

Declarations

Conflict of interest There is no conflict of interest.

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