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Atherosclerosis and chronic hepatitis C

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Article commented

Petta S, Torres D, Fazio G, Cammà C, Cabibi D, Di Marco V, Licata A, et al. Carotid Atherosclerosis and Chronic Hepatitis C: A Prospective Study of Risk Associations. *Hepatology* 2012; 55: 1317-23.

Comments

After the first report of an association of viral infection and atherosclerosis in 1970,[1] several studies have suggested that there is a link between arteriosclerotic disease and persistent infection or seropositivity of certain micro-organisms, such as *Chlamydia pneumoniae*, cytomegalovirus, Helicobacter *pylori*, and herpes simplex virus.[2–6] The pathogenetic mechanisms may vary and are still poorly understood. Evidence demonstrate that hepatitis C virus, alone or in association with other viral infections, is involved in the development and progression of carotid atherosclerosis.[7,8] Given their association with inflammation which is now seen as a key event in the atherosclerotic process. Infectious pathogens induce macrophage foam cell formation and induce activation of the immune response and potentiate the immune inflammatory reaction underlying atherosclerosis.[9] A retrospective analysis undertook a systematic review of the literature to study the association between HCV and carotid atherosclerotic plaques. A total of 18 studies in the English language were identified. All studies were designed with the intention of comparing carotid atherosclerosis between HCV positive and HCV negative patients, HCV positive patients were more likely to have a carotid plaque than HCV negative patients (48.2 *vs.* 20.7%, p = 0.05). Concluding that HCV positive subjects seem to have a higher likelihood of having carotid atherosclerotic plaques as compared to HCV negative individuals.[10]

In this study Petta, *et al*. evaluated the prevalence of carotid atherosclerosis compared with a control population in order to assess the potential association between atherosclerosis, host and viral factors, and liver histological features. In all, 174 consecutive biopsy-proven G1 CHC patients were evaluated by anthropometric and metabolic measurements and 174 patients attending an outpatient cardiology unit were used as controls. Intima-media thickness (IMT) and carotid plaques, defined as focal thickening of > 1.3 mm at the level of common carotid, were evaluated using ultrasonography. All G1 CHC biopsies were scored by one pathologist for staging and grading, and graded for steatosis. Carotid plaques were found in 73 (41.9%) G1 CHC patients compared with 40 (22.9%) control patients (P < 0.001). Similarly, G1 CHC patients had a greater IMT compared with control patients (1.04 ± 0.21 *vs.* 0.90 ± 0.16; P < 0.001). The authors find that older age (odds ratio [OR] 1.047, 95% confidence interval [CI]: 1.014-1.082, P = 0.005), and severe hepatic fibrosis (OR 2.177, 95% CI: 1.043-4.542, P = 0.03), were independently linked to the presence of carotid plaques. In patients ≤ 55 years, 15/67 cases with F0-F2 fibrosis (22.3%) had carotid plaques, compared with 11/21 (52.3%) with F3-F4 fibrosis (P = 0.008). By contrast, in patients > 55 years the prevalence of carotid plaques was similar in those with or without severe fibrosis (25/43, 58.1% *vs.* 22/43, 51.1%; P = 0.51). The authors concluded that severe hepatic fibrosis is associated with a high risk of early carotid atherosclerosis in G1 CHC patients.

Patients with chronic HCV infection, have a higher risk to develop steatosis, attributable to a variable combination of the mechanisms. Insulin resistance in the obese and in the lean subject, along with a direct effect of HCV on hepatic lipid metabo-

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lism that leads to triglyceride accumulation through inhibition of export proteins that are required for very low density lipoprotein (VLDL) assembly and secretion. HCV infection *per se* does not carry an increased risk of steatosis or insulin resistance, but is able to perturb glucose homeostasis through several direct and indirect mechanisms, leading to both hepatic and extra hepatic insulin resistance. Steatosis-related hepatic insulin resistance may also play a role through the profibrogenic effects of the compensatory hyperinsulinemia and provides a potential explanation for the association between G1 CHC infection and type 2 diabetes mellitus, steatosis, being both risk factors for developing atherosclerosis.[10-14] The oxidative stress has shown to play a primary role on the development of steatosis and insulin resistance.[14] Recent results indicate that seropositivity for HCV shows a positive association with carotid artery plaque and carotid intima-media thickening, independent from other risk factors for atherosclerosis.[15] A recent work found that HCV infection may be localized in plaque tissue, Accordingly, the detection of viral RNA in the plaque tissue of patients in the absence of detectable viremia points out the possibility of a compartmentalization of the virus in this district with pathogenetic consequences. This in turn suggests a role of HCV in carotid atherogenesis.[16]

In conclusion, the study conducted by Petta, *et al.,* is particularly interesting because they demonstrate that the presence of advanced hepatic fibrosis identifies a subgroup of G1 CHC patients at higher risk of atherosclerotic lesions. These findings confirm previous observations where this association was found. This novel work suggests that this subgroup should be carefully monitored in liver units, independently of their metabolic profile.

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