HEPATITIS - C VIRUS INFECTION, ENHANCING SILENT EPEDEMIC OF CORONARY ARTERY DISEASE

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INTRODUCTION

Hepatitis C virus, small, single stranded, RNA virus, identified for the first time in 1989, is a major health care concern worldwide but more so in developing countries like Pakistan [1] It has already infected more than 170 millions people worldwide (WHO1997) accounting for 3 % worldwide prevalence rate.

The reported seroprevalence in Pakistan ranges from 0.7 – 20 %, infecting more than 10 million people in Pakistan [1,2] This number continues to grow.[3]

The prominent genotype in Pakistan is type 3a (75-90%).[4] The striking feature of hepatitis C virus infection is the risk of persistent infection (of liver). Although, liver is the primary target of hepatitis C virus infection, most recently peripheral blood leukocyte and myocardium have been reported as a possible extra-hepatic site for viral replication.[5,6,7]

It has become increasingly evident that HCV infection is a systemic disease and can induce diseases of many organs. Hepatitis C related vasculitic, metabolic and endocrinal disorders have drawn attention of many researchers. Hepatitis C infection is known to be associated with several extra hepatic immune disorders including cryoglobulinaemia[9 to 11], sicca like syndrome that resembles Sjogren's [12] and membranous proliferative glomerulonephritis.[13]

The conditions that are less well documented to be related to hepatitis C virus infection are renal dysfunction, coronary artery disease and cerebrovascular disease.

However most recently many studies have reported evidence showing a relationship between hepatitis C virus infection, diabetes 36 to 40, hypertension[14], and other metabolic disorders 39 which are responsible for enhancing coronary artery disease many fold.

HEPATITIS – C VIRUS INFECTION AND RELATED CARDIO VASCULAR DISEASES.

Coronary artery disease is the most common heart disease with multifactorial etiology. Atherosclerosis being the principal cause has plagued human kind since ancient times. Its understanding has much evolved over centuries, traditionally being viewed as degenerative disease, is now considered a dynamic inflammatory and fibroproliferative process, triggered by cytokines and growth factors.[15-18]

In addition to other conventional atherogenic risk factors (Age, Sex, Smoking, Hypertension, Diabetes Mellitus and Dyslipidaemia), one of the most interesting development in the recent years has been the idea that infective agents may induce a proinflammatory state and have a crucial role in atherothrombosis[18-20].

The monoclonal theory, proposed first in 1970s has suggested a potential role of viral infection in atherosclerosis[19,31,32]. Since then many additional results have shown an association between infectious agents and atherosclerotic process[20-24]. Although other studies have shown contrary results,[27] most recent data have indicated that seropositivity for HCV infection may have a role in pathogenesis of carotid intima media thickening[25] and also affects the onset and development of coronary artery disease[26-28].

Hepatitis-C virus infection myocarditis and dilated cardiomyopathy

A pathogenic link between hepatitis-C virus infection and dilated Cardiomyopathy has been reported[7,8] both positive and negative strains of HCV have been isolated from the myocardial and peripheral blood mononuclear cells supporting the hypothesis of viral

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replication in extra hepatic sites and its related damage.

HCV related vasculitus (pathophysiology)

The mechanism for the development of angiitis may be either direct colonization of vasculature by the pathogens[19] or a stimulation of an inflammatory cascade[20], causing changes in the vessel wall, such as thickening, weakening, narrowing and scarring. Inflammation can be short term or long term. HCV related cryoglobulinaemia and immune complex mediated inflammation could be associated with endothelial damage and account for coronary artery dissection and therefore acute coronary syndrome[34-37] Anti-cardiolipin antibodies have been reported in 22% of patients with HCV positive serology and can be implicated in the pathogenesis of atherothrombosis.[41]

HCV infection and prevalence of other atherogenic risk factors

Some studies have reported higher prevalence of other atherogenic cardiovascular risk factors among individuals with HCV infection.[24-28]

HCV, Diabetes Mellitus and Metabolic Syndrome

It is suggested that there may be an association between HCV infection and diabetes mellitus, particularly type 2 (independent) for the presence of cirrhosis.

HCV infection induces steatosis and increases TNF-, both resulting in the development of insulin resistance and subsequent type 2 diabetes mellitus. The presence of diabetes mellitus and steatosis may enhance chances of atherosclerosis.[37-40]

The person with age over 40 years and HCV infection had 3.8 folds increased risk to have diabetes.[37] It has reported substantially that there is a higher incidence of type 2 diabetes mellitus for persons with recognized diabetic risk factors and HCV infection compared with those with similar diabetic risk factors but with no HCV infection. Patients who are euglycaemic but have insulin resistance and hyperinsulinemia may develops endothelial dysfunction and many of other clinically unmeasured risk factors such as prothrombotic state, pro-inflammatory state and increase oxidative stress which can lead to accelerated coronary artery disease course.[42] It is said "advance coronary artery disease has been traditionally considered as an absolute test and positive assay for HCV anti bodies".

HCV and hypertension

It is common in HCV associated membranous proliferative glomerulonephritis, present in majority of the patients at the onset of the disease and is often severe and difficult to control. Cryoglobulinemia patients present with more arterial hypertension vasculitus and albumenuria.[9-11,30]

Summary

Hepatitis C virus, an insidious disease, an evolving epidemic of new millennium, has been independently linked to Atherosclerosis affects the onset, development and progression of carotid atheroma[23,25] and coronary artery disease[24,26] (C vassale) in the present of HCV infection coronary artery disease have accelerated course and HCV + patients are much more likely to experience a fatal coronary event than are patients without HCV infection.

Its effects on cardiovascular system are both, direct like immune complex mediated vasculitus and Myocarditis and indirect one like metabolic autoimmune and endocrinal disorders. Patients with diabetes mellitus are not only on a higher risk to develop HCV infection but hepatitis C virus is an independent risk for developing diabetes mellitus and insulin resistance. Patients with cryoglobulinaemia are also on a higher risk to develop hypertension. These recent results linking HCV seropositivity to the presence of coronary artery disease, an emerging risk factor for atherosclerosis, an eminent idea of research has emboldened us to embark on such study, which was a time based and carried out in cardiology department at Mayo Hospital, Lahore. In our study, there was overall higher frequency of diabetics and hypertensive in HCV positive group (HCV, + vs. HCV- ve , P= 0.02, P= 0.05, respectively. For new onset diabetes and hypertension, statistically more significant difference was observed P=0.008, P=0.0001, skin vasculitic lesions, pruritis, mild renal

dysfunction, moderate anemia and raised ALT were marked in study group P1=0.01 P2=0.003, P3=0.001, P4=0.004, Considering coronary artery morphology, a statistical significant difference between the two groups when nature of coronary artery disease was studied. Disease was more complex. Lesions were long with main branches involvement and disease was diffuse in distal vessels making revascularization very difficult if not impossible. Diffuse ectasia with multi blockages was the prominent feature in HCV+ group. P=0.02.

Hepatitis C has definite link with the development of coronary artery disease. It not only affects the course of coronary artery disease directly but indirectly also through enhancing the development of other atherogenic risk factors many fold. We should review our understanding of coronary artery disease and look into other new possible emerging risk factors and intervene them in time so that we could prevent against the development of coronary artery and relieve the nation of economical burden being imposed by ischemic heart disease.

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