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HEV is one of the prominent infectious diseases in the developing nations, especially in India, where the infection spreads either in epidemics or in isolation, due to bad hygienic and living conditions and contaminated water. The HEV infection results into acute hepatitis and can be a cause for fulminant hepatitis during pregnancy. The pathogenesis of the virus and the mechanism(s) of the fulminant hepatitis have not been understood clearly. Over the past few decades, a correlation between the viral pathogenesis and virus-host interaction has been evidenced. Although a number of immune response studies are available in hepatitis B and hepatitis C viral infections, such studies of immune response in HEV infection are scanty. The available studies in HEV infection are restricted to the humoral response and have demonstrated the presence of high titers of anti-HEV IgM, IgG and IgA antibodies during the course of infection. There is a paucity of information even to understand the role the complement system plays in the host defense in HEV infections, before one attempts to explore other important aspects of immune response in HEV infection. Since the infection is intracellular, a study of cell mediated immune response in HEV infection is required. It is still not clear if a particular pattern of the cytokine release from the polarized T cells influences the type of immune response in favour of Th-1/ Th-2/ Th-3 in modulating the host defense mechanism and the ultimate outcome of the infection in HEV cases. Recognition of immunodominant epitopes in ORF2 and ORF3 (two of the three open reading frames known) antigens of HEV suggests that pORF2 and pORF3 could have the potential to exhibit specific immune response which contributes to viral pathogenesis.

The differential susceptibility to hepatitis due to HEV infection, an another dimension of pathogenesis, could also be explored in terms of differential genetic backgrounds, leading either to a high or low level of important host proteins, involved in self-defense or pathogenesis. In recent years a number of reports have addressed the possibility of an influence of genetic polymorphism within the regulatory regions of cytokine genes on the level of their expression and the resultant immune response. Till now a large number of candidate genes involved in immune response and with polymorphism have been suggested to be associated with different infectious diseases. Further, it has also been observed that some
of these polymorphisms at times are confined to a given population group. With this background, it was pertinent to explore if there was an association of known and new polymorphisms in the studied regions, with the susceptibility to hepatitis E in Indian patients.

The present work to ‘Study the T cell response to Hepatitis E virus antigen in patients with acute hepatitis-genotyped for cytokines’ was undertaken to have an initial understanding of the pathogenesis of hepatitis E infection, laying down the following objectives:

- **study the role of complement system and nitric oxide in the pathogenesis of acute hepatitis with and without HEV infection**, where levels of C4 and C3 complement components were estimated semi-quantitatively and nitrite ions assessed in the sera samples of prospective and retrospective acute hepatitis patients and normal subjects.

- **study the proliferative response of peripheral blood mononuclear cells (PBMCs) of normal subjects and acute hepatitis patients to HEV antigens.** It was further proposed to study the proliferative response of peripheral blood mononuclear cells (PBMCs) of patients with acute hepatitis (prospective and retrospective) and healthy controls to hepatitis E virus antigens (baculovirus expressed partially deleted ORF2 and *E. coli* expressed ORF3). Proliferation of cells was assessed in terms of stimulation index (S.I).

- **study the lymphocyte mediated expression of cytokine (IFN-γ, IL-4 and TGF-β1) profile.** It was proposed to find out if the differential expression of these cytokines influenced the type of immune response in both retrospective and prospective patients with acute hepatitis in comparison to healthy controls. The culture supernatants of mitogen (PHA) and HEV antigen (pORF2 and pORF3) stimulated PBMCs were assessed for IFN-γ, IL-4 and TGF-β1 as an indicator of Th-1, Th-2 and Th-3 cells, respectively.

- **study the association between cytokine (IFN-γ, IL-4, IL-6 and TGF-β) gene polymorphism and susceptibility to hepatitis E infection.** It was proposed to genotype both patients and controls to assess if the changes in the level of expression of cytokines under study showed an association with the existence of such polymorphisms. For this, certain
relevant candidate genes, IFN-γ (Th-1 type cytokine), IL-4 (Th-2 type cytokine), IL-6 (Th-2 type cytokine and a possible player in hepatic regeneration) and TGF-β (Th-3 type cytokine), were chosen and their regulatory regions subjected to PCR-SSCP (single stranded conformation polymorphism) – Sequencing and PCR-SSLP (simple sequence length polymorphism), to establish the preponderance of known and novel polymorphisms in patients and healthy controls.