Introduction
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Dengue is the most important human viral disease transmitted by arthropod vectors. Annually there are an estimated 50–100 million cases of dengue fever (DF) and 250,000 to 500,000 cases of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) occurring in the world (Halstead, 2007). Dengue infection is endemic to many parts of India, and epidemics are becoming more frequent. Delhi has experienced seven outbreaks of dengue virus infection since 1967 with the last reported in 2006 (Bharaj et al., 2008). In 2003, major outbreaks of DF and DHF have been reported from various parts of the country (Kabilan et al., 2003) and Puducherry was one among them (Hoti et al., 2006).

Dengue fever, DHF and DSS are caused by the four dengue serotypes DEN 1, 2, 3, and 4, which are closely related antigenically. Infection with one serotype provides life-long immunity to that virus but not to other serotypes. Dengue viruses are transmitted to humans through the bite of infected female mosquitoes of the genus *Aedes* (A). The primary mosquito vector is *A. aegypti* and *A. albopictus* (Weaver and Barrett, 2004). Only the females seek blood meals, and they feed primarily during the day (Solomon and Mallewa, 2001). After virus incubation for 8-10 days, an infected mosquito is capable of transmitting the virus to susceptible individuals for the rest of her life. *A. aegypti* breed in collections of clean water (storage jars, containers, etc.).

Dengue hemorrhagic fever has been classified into four grades: the mildest is grade I and the most severe is grade IV. Extensive plasma leakage into various serous cavities of the body in DHF grades III and IV may result in profound shock, the DSS. The classical features of DHF are increased capillary permeability without morphological damage to the capillary endothelium, thrombocytopenia, altered number and functions of leucocytes, and increased haematocrit (Halstead, 1993, Chaturvedi et al., 1997).

For years, DHF pathogenesis has been a controversial matter and current hypothesis is that it occurs as a consequence of a very complex mechanism where virus, host, and host immune response interact to give this severe disease (Guzman and Kouri, 2008). In endemic areas, only a relatively small proportion of affected persons develop
DHF, which suggests that there are host risk factors for the development of the complications among the infected individuals (Gubler, 1998) Within the host genetic risk factors, mechanisms involving human leucocyte antigen (HLA) alleles or non-HLA alleles in determining resistance, susceptibility or the severity of dengue viral infection have been reported (Chaturvedi et al., 2006)

The pathogenesis of DHF is not well understood Virus-specific CD8+ T cell responses have been reported to play essential roles in the pathogenesis of dengue infection (Livingston et al., 1995) HLA class I genes encode molecules that present mainly host- or microbe-derived antigenic peptides to CD8+ T cells During this step, the transporter associated with antigen processing (TAP) protein translocates such peptides from the cytosol into the endoplasmic reticulum where the peptides become associated with class I molecules Recent studies on mutation analysis of the TAP gene have shown that even a single substitution of an amino acid can result in a dramatic change in substrate selectivity (Momburg et al., 1996) Although some HLA class I A, B and II DR molecules were reported to play important roles in the severity of dengue viral infection, the precise mechanism of these associations remains unclear (Chaturvedi et al., 2006) Because human TAP genes are located between HLA-DP and HLA-DQ in the class II region and play major role in class I antigen processing, genetic polymorphism of TAP might have association with the severity of dengue viral infection Hence for the first time genotyping of both TAP 1 and 2 loci was carried out in different clinical spectrum of dengue infected individuals in the present study

Similarly the pathogenesis of thrombocytopenia in severe dengue viral infection is not clearly understood One of the important and possible mechanisms that have been postulated for thrombocytopenia is destruction of thrombocytes by autoimmunity, abnormal activation and aggregation of platelets (Osu and Inoves, 2003) One of the most frequent alloantigen that is associated with immune thrombocytopenia is Human Platelet Antigen 1 (HPA 1) HPA-1a/b polymorphism was identified as a single nucleotide change causing an amino acid substitution Numerous studies examined the role of HPA 1 polymorphism in a wide variety of autoimmune thrombocytopenia (Rozman, 2002) Likewise abnormal platelet activation and aggregation was found to be associated with
polymorphism of another glycoprotein (GP) complex called HPA 2 (Murata et al., 1992)
Therefore in the present study typing of HPA1 and 2 gene polymorphisms was undertaken for first time among dengue infected individuals in explaining the etiopathogenesis of severe dengue disease

Accumulating experimental evidences have shown that reactive oxygen species (ROS) play a key role in the pathophysiological pathways of a wide variety of clinical viral diseases (Schwarz, 1996) While Oxidative stress also appears to play an important role in the pathogenesis of dengue fever, its implication in the evolution of DHF and DSS is not yet studied (Gil et al., 2004) The possibility of oxidative stress due to dengue viral replication in macrophages, besides killing the target cells by apoptosis, can also directly up regulate production of certain proinflammatory cytokines that result in an exacerbation of dengue disease However, no in vivo studies are available to associate the oxidative stress and inflammatory response in dengue Therefore the impact of oxidative stress and its association with cytokines levels were studied in different clinical groups of dengue infection

In view of the above findings there exist several gaps in the knowledge on the dengue pathogenesis and immunogenetics Hence the present study was carried out to assess the role of host factors such as genetic, inflammatory and biochemical risk factors in the development of severe form of dengue disease

In order to achieve the aim, the following objectives were carried set

1. *Investigation of the role of TAP and HPA 1 and 2 gene polymorphisms in the clinical spectrum of dengue infection*

2. *Assessment of the oxidant/antioxidant status and proinflammatory cytokine levels in blood and the possible association between them in relation to the pathogenesis of severe dengue infection*