SEVERITY OF DENGUE DISEASE AND THE ROLE OF DIFFERENT SEROTYPES AND GENOTYPES OF THE CAUSATIVE VIRUSES

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ABSTRACT

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The pathogenesis of dengue haemorrhagic fever (DHF) or severe dengue disease is still controversial. Recent reviews have established that both viral and immunological factors are involved in the pathogenesis of severe dengue disease. Recurrent epidemics that have occurred in Sri Lanka since 1989, raises the question as to whether or not viruses have specific genetic characteristics which increase their associated disease severity and also whether or not the viruses evolve in situ in the country or are continually imported from other localities.

Serum samples (day 1-4 of fever) from patients with suspected dengue fever were subjected to reverse-transcriptase polymerase chain reaction to detect the viral genome. The data collected during the 50 month study period starting from January

2003 was compared with the cases reported to the Epidemiology Unit, Ministry of Health, Sri Lanka. RT-PCR positive samples were subjected to a semi-nested multiplex PCR to determine the serotype of the causative viruses. Selected set of samples covering the largest outbreak in the year 2004, were subjected to virus isolation on C6/36 cell lines. In phylogenetic analysis, Sri Lankan dengue virus isolates from years 1983, 1984, 1989, 1990, 1992, 1996, 1997, 2003 and 2004 representing all four serotypes were included to understand the genetic variations over time. Dengue cases confirmed by RT-PCR treated inward were followed up in the collaborating hospitals.

Study data which reflects and represents the National data can be applied to understand the dengue epidemiology and can be used as a sentinel site/tool to monitor dengue activity in the island. In the study, highest dengue activity (35%) was observed in young adults (20-35 years) and in younger children below 5 years (13%). 17% of patients have developed hemorrhagic fever and 48% patients with severe manifestations had been potential candidates to develop hemorrhagic fever.

Revision of WHO criteria for classification of dengue disease is suggested as the strict application of the WHO criteria fails to categorize a significant number of patients with severe manifestations without bleeding diathesis.

All four serotypes were found responsible for infections, while 86% of the causative viruses were either DENV2 or DENV3. Severe dengue disease was found with all four serotypes. However, clade replacement of DENV3 genotype IIIA with IIIB was demonstrated to have a major role in severe disease and increased transmission after 1989. The study demonstrates that the step increase in cases after the year 2000 was accompanied by the appearance of another new clade of genotype III viruses that have replaced the genotype IIIB viruses. The South pacific genotype of DENV1 was replaced by the African/American subtype after 1992. There is no evidence of recent introduction/evolution of DENV2 Indian Subcontinent genotype. Individuals infected with DENV2 South East Asian subtype viruses who developed severe disease may have been exposed to the African/American genotype of Den 1 viruses previously. DENV4 South East Asian type appears to have been established from 1978 to 2004 in Sri Lanka and a transient introduction of Indonesian type was seen in 1992.

Virus serotype and genotype are only partially responsible for severe dengue disease. Host factors such as individual's immune status, regulatory mechanisms and pre-existing antibodies may be equally important to infecting serotypes and genotypes in dengue disease severity.