The curse of dengue

Dengue fever (DF) and dengue haemorrhagic fever (DHF) have arrived to stay with vengeance in this country. Is it unexpected? No, we are not surprised as all the risk factors that promote spread of dengue virus (DV) are present here, and in plenty. The risk factors for DF/DHF are infestation with *Aedes* mosquito, hot and humid climate promoting mosquito breeding, mosquito density, the water storage pattern in the houses, population density and large movement of people towards urban area. This country has witnessed extensive construction work, for houses, malls, national highways network and special economic zones. These activities result in dumping of construction and demolition materials forming small pits and pockets for rain water collection. Due to erratic and scanty water supply the households are forced to store portable water in containers without a lid thus providing ideal sites for *Aedes* breeding. Dengue viruses are of four serotypes (1 to 4) and the presence of more than one serotype in a population is a risk factor for DHF. The co-circulation of multiple DV serotypes in the same region has been a common knowledge in several countries including India. Using a modified multiplex reverse transcription-polymerase chain reaction assay, concurrent infections by two different serotypes of dengue virus have been shown to occur in the same patient. Such concurrent infections by two dengue viruses may also increase the severity of the disease. Genotypic studies have shown that the more virulent Asian strain of DV is different from the milder American strain which suggest a role for viral genetics in DHF. Emergence and re-emergence of DF and DHF continue to be a global challenge.

The evolution of genetics of hosts, pathogens and vectors have been phenomenal and the extensive growth of genetic studies over the years has greatly increased our understanding of the transmission and pathogenicity of infectious diseases. The profound influence of the host’s genetic make-up on resistance and susceptibility to DHF has been established in numerous studies.

Dengue is found in tropical and sub-tropical regions around the world, predominantly in urban and semi-urban and now in rural areas also. Humans are the main amplifying host of the virus. Recovery from infection by one type of DV provides lifelong immunity against that serotype but confers only partial and transient protection against subsequent infection by the other three. Halstead described antibody-dependent enhancement (ADE) of infection, in which DV uptake and replication in macrophage is increased by immune sera (IgG), and this phenomenon has later been observed for a number of viruses. The sequential infection increases the risk of DHF specially if infection with DV-1 is followed by DV-2 or DV-3. Viral virulence and immune responses have been considered as two major factors responsible for the pathogenesis of DHF. Virological studies are attempting to define the molecular basis of viral virulence. The immunopathological mechanisms appear to include a complex series of immune responses. A rapid increase in the levels of cytokines and chemical mediators apparently plays a key role in inducing plasma leakage, shock and haemorrhagic manifestations. It is likely that the entire process is initiated by infection with a so called virulent dengue virus, often with the help of enhancing
antibodies in secondary infection, and then triggered by rapidly elevated cytokines and chemical mediators produced by intense immune activation. However, understanding of the DHF pathogenesis is not complete.

The first major epidemic illness that was clinically compatible with dengue occurred in Madras (now Chennai) in 1780 and later on spread to all over the country. DV was first isolated in Japan in 1943 and one year later at Calcutta in 1944 from the blood of US soldiers. DHF was first recognized in 1950s during the dengue epidemics in the Philippines and Thailand and quickly spread to other parts of the world11. Only nine countries had DHF epidemics before 1970. The prevalence of dengue has grown dramatically and the disease is now endemic in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, Southeast Asia and the Western Pacific, the last two are most seriously affected. Extensive epidemics of DF occurred in India, the early ones were at Calcutta and south India in 196312,13. Then DF became endemic all over India14,15. DHF was present in the neighbouring countries for a long time but the first extensive epidemic of DHF occurred only during 1996 in the northern India16,17. One does not know what prevented it from coming to this country till 1996 as all the risk factors were present.

Some 2500 million people - two fifths of the world’s population - are now at risk from dengue. According to the WHO estimates made in 2002 there may be 50 million cases of dengue infection worldwide every year. An estimated 500,000 cases of DHF require hospitalization each year, of whom a very large proportion are children18,19. The year 2001 witnessed unprecedented global dengue epidemic activity in the American hemisphere, the Pacific islands and continental Asia. During 2002, more than 30 Latin American countries reported over 1000000 DF cases with large number of DHF cases2,18. Over the past two decades, DV type 3 has caused unexpected epidemics of DHF in Sri Lanka, East Africa and Latin America. Isolates from these geographically distant epidemics are closely related and belong to DV serotype 3, subtype III, which originated in the Indian subcontinent. The emergence of DHF in Sri Lanka in 1989 correlated with the appearance of a new DV serotype 3, subtype III variant which forms genetically distinct group19. This variant spread from the Indian subcontinent into Africa and from there into Latin America in the mid 1990s20. The 1996 epidemic in India was mainly due to DV serotype 216,17 but since 2003, epidemics appear to be mainly due to DV serotype 3, subtype III21. The present DHF epidemic (during 2006) in India appears mainly due to DV serotype 3, though other serotypes are also present.

Early diagnosis of DV infection is important and can be established with easily available laboratory tests. Increased haematocrit value (>20%) and a positive tourniquet test indicate that the patient should be under close surveillance for early signs of DHF while negative test does not rule out dengue infection. Low platelet counts do not predict clinically significant bleeding in dengue. It follows that platelet or blood transfusions should not be administered based upon platelet count alone. DHF or dengue shock syndrome cases frequently have compensated consumptive coagulopathy that seldom requires treatment. Bleeding is most likely caused by activated platelets resulting from damaged capillary endothelium. There is no specific treatment for dengue fever. However, careful clinical management frequently saves the lives of DHF patients. With appropriate intensive supportive therapy, mortality may be reduced to less than 1 per cent.

Vaccine development for dengue and DHF is difficult because any of four different viruses may cause disease, and because protection against only one or two dengue viruses could actually increase the risk of more serious disease. However, efforts are being made for the development of vaccines that may protect against all four dengue viruses. Several promising vaccine candidates in the form of live attenuated and chimeric vaccines have been developed and are currently in human clinical trials. However, significant practical, logistic, and scientific challenges remain before these vaccines can widely
and safely be applied to vulnerable populations. Dengue continues to be a global challenge because the pathogenesis of DHF is not fully understood, there is no immediate prospect of a vaccine and the mosquito control measures are inadequate. In absence of a vaccine or drug, the dengue disease can be managed successfully by preventing serious illness through patient follow up and monitoring danger signals so that aggressive intravenous rehydration is initiated to prevent shock and complications, such as massive haemorrhage and disseminated intravascular coagulation, etc. At present, the only method of controlling or preventing DF and DHF is to combat the vector mosquitoes. The wide-spread DHF epidemics reinforce the belief that DHF has come to stay in this country and will continue to spread to newer areas unless mass education on the vector control measures in and around households are taken up on war footing.

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