Review Article

Dengue haemorrhagic fever and the dengue shock syndrome in India

R. LALL, V. DHANDA

ABSTRACT
The clinical spectrum of dengue fever ranges from asymptomatic infection through severe haemorrhage and sudden fatal shock. Increased capillary permeability is the diagnostic feature of dengue haemorrhagic fever (DHF). The pathophysiology of DHF/dengue shock syndrome (DSS) is related to sequential infection with different serotypes of the virus, variations in virus virulence, interaction of the virus with environmental or host factors and a combination of various risk factors. Infection due to low virulence strains is assumed to be the reason for the infrequent incidence of serious dengue disease in India. Since all four serotypes of the dengue virus have been implicated in various outbreaks in this country and several outbreaks of DHF/DSS have been recorded since the first report in 1963, further epidemics of the disease are likely. The situation is aggravated by the recent emergence of DHF/ DSS in Sri Lanka. In view of the potential of this disease to spread, effective preventive and control measures should be a priority.


INTRODUCTION
Dengue haemorrhagic fever (DHF) is clinically defined as an illness that worsens two days or more after its onset, and is characterized by a haemorrhagic diathesis, hypoproteinaemia and a tendency to develop a shock syndrome that may be fatal.1 The World Health Organization (WHO) case parameters for DHF include: (i) fever; (ii) haemorrhagic manifestations, including at least a positive tourniquet test (except in patients in shock), and either major or minor bleeding phenomena; (iii) thrombocytopenia (platelet count ≤100 000/cmm); and (iv) haemoconcentration (increase in haematocrit by 20% or more relative to baseline values, or objective evidence of increased capillary permeability).2

The dengue shock syndrome (DSS) consists of haemorrhagic fever and shock (hypotension or a pulse pressure of 20 mmHg or less) and haemoconcentration (haematocrit at least 20% greater than the initial value). This syndrome is caused by increased vascular permeability and resultant intravascular hypovolaemia.3,4 Cases of severe haemorrhage or even death caused by dengue infection without evidence of increased capillary permeability are not currently classified as DHF according to WHO criteria.5

Dengue infection is endemic in India and outbreaks have so far been confined to urban areas. The majority of these have been of the classical dengue fever type. There has been a spurt of outbreaks of dengue fever in the rural areas. There also appears to be a marked increase in DHF during the outbreaks in rural as well as in urban areas.6-9 After HIV-1 infection, DHF is now the largest emerging viral disease globally.10 The present review deals with the occurrence of DHF/DSS in different parts of India.

EPIDEMIOLOGY
Dengue haemorrhagic fever, the most prominent of the haemorrhagic fevers of Southeast Asia and India, is an acute, infectious, urban, mosquito-borne disease. It is caused by four serotypes of the dengue virus transmitted principally by the domestic mosquito, Aedes aegypti. Classical dengue fever is endemic in many parts of India except the Himalayan and other mountainous regions where conditions are not conducive to the propagation of its vector. The disease has been prevalent in India for over two centuries,11,12 but is recognized only when outbreaks occur. Serological surveillance against dengue viruses in India and the ecology of the vector have been reviewed in the past.13-15 The outbreaks in India occur mostly during or after the rainy season, which coincide with the rise in the vector population. Outbreaks have also been reported during the dry summer months when widespread storage of water for domestic purposes causes a rise in the vector population.16,17 Many outbreaks have been reported since 195618 with fairly recent ones from Delhi (1988,19-21 199123), Calcutta (199022), Madras (1987, 198923) and Vellore (199023).

Unlike the other countries of Southeast Asia, DHF in India has usually not been a serious problem. Multiple aetiological agents including the Chikungunya virus were identified during epidemics of haemorrhagic fever. This is thought to be due to genetic differences between the Southeast Asian and Indian dengue strains.24 The emergence of the DHF/DSS epidemic in Sri Lanka provides evidence that the syndrome is not host-related but virus-related.24 It now appears that Indians and Southeast Asians are equally susceptible to severe dengue illness, and virus strain differences must be the reason for the low incidence of DHF/DSS in India. The observation of DSS occurring in Indian children residing in a Yangon community during 1984-85 were no different in incidence from the disease occurring in Myanmar children. This disproves the hypothesis that Indians may be genetically less susceptible to DSS than other populations.25

Dengue haemorrhagic fever was first reported in India from...
Table I. Dengue haemorrhagic fever and dengue shock syndrome in India.

<table>
<thead>
<tr>
<th>Place</th>
<th>Year</th>
<th>Dengue virus serotype incriminated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcutta26-31</td>
<td>1963</td>
<td>DEN-2</td>
</tr>
<tr>
<td>Vellopatnam32,33</td>
<td>1964</td>
<td>DEN-2</td>
</tr>
<tr>
<td>Asansol34</td>
<td>1967</td>
<td>DEN-2, 4</td>
</tr>
<tr>
<td>Kanpur35,36</td>
<td>1968</td>
<td>DEN-4</td>
</tr>
<tr>
<td>Vellore37</td>
<td>1968</td>
<td>DEN-3, 4</td>
</tr>
<tr>
<td>Ajmer38</td>
<td>1969</td>
<td>DEN-1, 3</td>
</tr>
<tr>
<td>Kanpur39</td>
<td>1969</td>
<td>DEN-2</td>
</tr>
<tr>
<td>Delhi40</td>
<td>1970</td>
<td>DEN-1, 3</td>
</tr>
<tr>
<td>Jalore41</td>
<td>1985</td>
<td>DEN-2</td>
</tr>
<tr>
<td>Delhi42-43</td>
<td>1988</td>
<td>DEN-2</td>
</tr>
<tr>
<td>Vellore44</td>
<td>1990</td>
<td>Not established</td>
</tr>
</tbody>
</table>

Calcutta.26 The clinical picture was similar to the Thai haemorrhagic fever. Since then, all outbreaks of DHF and DSS have been recorded in India (Table I). Outbreaks of haemorrhagic fever in which dengue viruses were isolated have been broadly labelled as DHF. However, the distinctive pathophysiological change, i.e. leakage of plasma as manifested by a rising haematocrit value and haemoconcentration and the use of the criteria for a clinical diagnosis of DHF/DSS laid down by the WHO in 1986,2 were not adhered to in establishing the diagnosis of DHF/DSS in the cited reports. The criteria for clinical diagnosis are: (i) acute onset, high grade, continuous fever lasting for 2–7 days; (ii) haemorrhagic manifestations including at least a positive tourniquet test; (iii) enlargement of the liver; and (iv) shock.

Thus, adults with dengue infection as well as, for instance, peptic ulcer and gastrointestinal haemorrhage may have been incorrectly included as having DHF/DSS. The WHO criteria for diagnosing DHF/DSS have been applied only in the outbreaks in Delhi (1988) and Vellore (1990).

In the first reported epidemic in Calcutta during 1963, clinical severity was more pronounced in the younger age groups. In a study of 54 cases (33 males and 21 females) reported by Aikat et al.,26 the largest number were between 11 and 20 years of age. There were 3 deaths—2 girls below 10 years of age and a male aged 18. The disease was reported from Vishakapatnam in 1964,32,33 where 107 cases consisting of 79 males and 28 females were studied. The affected age group was between 12–30 years and there was no death. An outbreak occurred in the town of Asansol in West Bengal in 1967.34 Among the 77 cases studied, there were 64 males and 13 females. There was no death, though the shock syndrome was observed in a male aged 25 years. In the Kanpur epidemic of 1968, there were 12 deaths among 224 cases of DHF.35,36 The youngest case was 2 years old and the oldest 65. Adolescents and young adults were most frequently affected. Of the 224 cases, 58 were in the 11–20 years age group and 89 were between 21 and 30 years of age. During the same year, there was no death among 125 cases in a DHF outbreak in Vellore.37 During 1969, among 97 cases studied in an outbreak in Ajmer, 2 cases of clinical encephalitis were seen.38 Dengue virus serotype 3 was isolated from the cerebrospinal fluid of one of them. No shock syndrome was seen. In the second outbreak of DHF in Kanpur in 1969, no mortality was reported among the 48 cases studied.39 An important finding was that dengue viral isolates produced lethal sickness in infant mice during the first or second passage.

In 1970, in a DHF outbreak in Delhi 4 deaths were reported among 273 cases.40 Almost all age groups were equally affected, females being affected more frequently than males. Jallore in Rajasthan suffered an outbreak of DHF in 1985.41 Among 110 cases (80 males, 30 females) reported, there were 5 deaths. Involvement of the central nervous system was noted in 3 patients who had encephalitis with tonic spasms and delirium. A relatively high incidence (2.7%) of encephalitis indicated greater virulence of the virus or increased susceptibility of the population during the outbreak. Dengue encephalopathy has also been reported on several other occasions from India,21,42-45 Indonesia,46,47 the Central Pacific48 and Greece.49 In the DHF epidemic of Delhi in 1988,19 among 21 children studied in a hospital (14 girls and 7 boys between 6 and 12 years of age), a clinical diagnosis of Grades III and IV severity was made in 14 and 7 cases respectively. There were 7 deaths and disseminated intravascular coagulation (DIC) was seen in one case. All the cases of DHF in 1988 were presumed to be the result of secondary infection in individuals sensitized by primary infection with dengue serotype 2 in the 1982 epidemic. An increased level of haemagglutination inhibition (HI) antibody against the dengue serotype 2 was seen in the first blood sample taken during the 1988 epidemic. In another report during the same year, 24 cases were found to be between 6 and 10 years of age.20 The case fatality rate was 13% in both the reports.

An epidemic involving 19 cases occurred in and around Vellore town, the North Arcot Ambedkar district in Tamil Nadu and adjoining districts in Tamil Nadu and Andhra Pradesh during June through November 1990,23 though isolated cases of DHF/DSS had been reported earlier in this region.37 The patients included 13 girls and 6 boys, the ages ranging from below 1 year to 12 years with most patients under six years of age. Spontaneous haemorrhage from various sites took place in almost all the cases. Because of cross-reacting epitopes, the identity of the serotype(s) of the virus responsible for this epidemic could not be established.

The rate of DHF among dengue-infected individuals varies with the underlying risk factors and the infecting virus strain.50 Estimates of this rate have ranged from 1 to 7 DHF cases per 100 dengue infections.51,52

RISK FACTORS

The virulence of the circulating strain is an important element in the analysis of an epidemic,53 with increased virulence of certain strains being postulated as the cause of epidemic DHF/DSS.54 Dengue virus strains isolated from patients with DHF/DSS are more virulent in the laboratory compared with strains obtained from patients with milder disease.55,56

Pre-existent dengue immunity as detected by conventional serological techniques was a significant (odds ratio ≥6.5) risk factor for the development of DHF.57

Race is an individual risk factor since DHF/DSS has been found to be more prevalent in whites than in blacks.58

The specific sequence of DEN-1 followed by DEN-2 appeared to be associated with the greatest risk for DSS. Secondary infection with DEN-2 which followed primary infections with DEN-1, DEN-3 or DEN-4 was a risk factor for DSS. The risk of DSS is only during the second infection and not in the subsequent ones. It is not known if all DEN-2 types are equally prone to cause DSS if preceded by DEN-1.59

Chronic diseases such as bronchial asthma, diabetes mellitus and anaemia are additional risk factors. Enhanced DEN-2 activity has been observed in leukocytes from asthmatic patients compared to healthy persons, supporting the fact that bronchial asthma is a risk factor for DHF/DSS as seen on analysis of epidemiological data.60
A genetic risk for DHF has been suggested which may be an important factor. HLA-A and -B typing on lymphocytes has shown a positive association for HLA-A2, and HLA-B blank and a negative relationship for HLA-B1.

Maternal dengue antibodies play a dual role by first protecting and later increasing the risk of DHF/DSS by DEN-2. In infants who developed DHF/DSS, there was a strong correlation between the mother’s DEN-2 neutralizing antibody titres and infant’s age at the time of onset of severe illness.

VECTOR

_Aedes aegypti_ is the principal vector of the disease in India. DEN-1 and DEN-4 viruses were first isolated from pools of female _Aedes aegypti_ in Vellore. All the four serotypes were subsequently isolated from mosquito pools in the Vellore epidemic. Studies have shown that the onset of an epidemic parallels the build up of mosquito population density. _Aedes albopictus_ has been considered to be a viable vector of the dengue virus in India though its role has not been established. The DEN-4 virus has been isolated from _Aedes albopictus_ at Asansol in West Bengal.

PATHOGENESIS

There are several theories to explain the pathogenesis of DHF/DSS. Secondary infection with a heterologous dengue serotype induces hypersensitivity resulting in DHF. Non-neutralizing antibodies to the dengue virus enhance viral uptake and replication in monocytes. The shock syndrome associated with DHF results from an antibody-dependent enhancement (ADE) phenomenon.

An alternative hypothesis proposes that haemorrhage and the shock syndrome are the direct and indirect consequences of complement activation. However, during an epidemic in Bangkok, children exhibited DSS even on primary exposure to dengue infection. In India, in contrast, even the existence of all four serotypes of the virus in Vellore failed to induce DHF.

PREVENTION AND CONTROL

The principal vector (_Aedes aegypti_) breeds primarily in man-made containers such as water storage vessels, old tyres, disused air-coolers, air-conditioners and flower vases in and around human dwellings. Elimination of these breeding sites is an effective and definitive method for controlling the vector and preventing the disease. New efforts are focusing on community education and behaviour modification in an attempt to control the vector through breeding site reduction.

Conventional antimosquito measures, such as fogging with insecticides like malathion and/or space spraying with pyrethrum, have not been found suitable for vector control although the larvicidal agent temephos SG has been found to be useful in some areas.

There is no dengue vaccine available for use, though research continues on the development of a safe and effective tetravalent vaccine that would circumvent the potential hazards predicted by the immune enhancement theory. Concurrent isolation of DEN-1 and DEN-4 serotypes from a 16-year-old patient in Puerto Rico who suffered only a mild attack of dengue augurs well for a multivalent vaccine. In epidemic situations, fogging with insecticides may be useful, but currently the most effective way to avoid infection is through the use of insect repellants and other mosquito barriers.
LALL, DHANDA: DENGUE HAEMORRHAGIC FEVER