Personal Practice

Dengue Viral Infection

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Dengue viral infection results in a spectrum of disease-on the milder side is dengue fever characterized by biphasic fever, myalgia, arthralgia, leukopenia and lymhadenopathy, while on the other extreme is dengue hemorrhagic fever representing an often fatal disease characterized by hemorrhages and shock syndrome(l) The disease, especially the severe form, has a predilection for the pediatric age group Over half of the reported cases of dengue viral infection and 13% of the related deaths in a recent epidemic in Delhi were seen in children less than 12 years of age(2)

Etiology

The dengue virus responsible for the disease belongs to class of flavivirus family Togaviridae and four distinct antigenetically related subtypes 1,2,3 and 4 have been known Togavindae are small to medium sized 25-50 nm diameter, spherical enveloped viruses having a genome of linear single stranded RNA Togavindae family contains four genera - Alphavirsues (Group A arboviruses), Flaviviruses (Group B arboviruses), Rubiviruses and Pestiviruses Within the Flavivirus group, there are more than 60 viruses, out of which half are mosquito-borne, one-fourth are tick-borne, while the reminder have no known arthropod vector(3)

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Epidemiology

Dengue viral infection has been known since the 19th century The Calcutta epidemic of Dengue fever in 1872 was probably the first recorded one from India(4) It is endemic in South-East Asia including India, East and West Africa and Caribbean islands and is now invading the new territories including many states of USA(5) Until 1970, only 9 countries had faced epidemics of dengue hemorrhagic fever, now at least 38 countries have experienced them(6)

In India, dengue epidemics have been more common m the last four decades *(Fig* 2)(2,7-16) In 1950s, the viral infection was more prevalent along the east and the west coast of the Indian peninsula(10) By now, dengue epidemics have been reported from all over India except Kashmir and the Himalayan region(16) The most recent epidemic centered around the Indian capital, New Delhi(2)

Dengue viruses are transmitted by the mosquitoes of stegomyia family *Aedes aegypti* is the principal vector, although dengue outbreaks have been attributed to *Aedes albopictuss, Aedes polynesiensis* and several species of *Aedes sctellaris* complex(3) *Aedes aegypti* are widely distributed in India These are peri-domestic mosquitoes and are most abundant during the rainy days Females are fearless biters and bite during the day They do not fly over

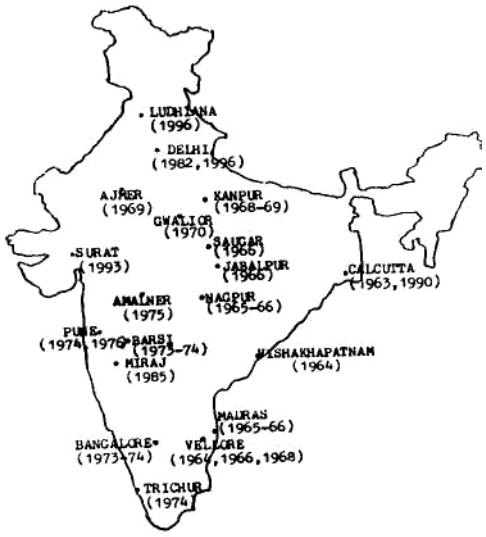

Fig. 1. Epidemics of dengue viral infections India, (Modified from Ref. 16).

long distances and this factor can facilitate their eradication(17).

Epidemic transmission of Dengue requires a favorable temperature (> 20° C) and stagnant water for breeding of *Aedes aegypti*. The environmental temperature has been shown to affect the transmission dynamics of dengue infection-a higher temperature within range of mosquito viability leads to more infectious mosquitoes which bite more frequently(18).

The reservoir of infection is both man and mosquito. The transmission cycle is 'man-mosquito-man', although in jungle settings, probably the monkeys are also responsible for maintaining this infection cycle(19). The Aedes mosquito becomes infective by feeding on a patient during viremia (from a day before onset to the fifth day of illness). The virus multiplies in its salivary glands. After an incubation period of 8 to 10 days, the mosquito becomes infective and is able to transmit the disease. Once the mosquito becomes infective, it remains so for life(20).

Several factors are probably responsible for the spread of dengue. The II World War in the eastern sector of India followed by prolonged war in the Indo- Chinese peninsula caused major upheavels in the population structure and habitation. Migration to cities and consequent urban degradation, overcrowding, scarcity of water and consequent storage of water in whatever form possible-have all contributed to spread and continued maintenance of dengue vector and the virus(21).

Dengue hemorrhagic fever (DHF) occurs where multiple types of dengue viruses are simultaneously or sequentially transmitted, as seen in hyper-endemic regions. The severe illness seen in DHF is thought to be due to a secondary dengue infection with heterologous serotype. The first infection probably sensitizes the patient, while the second appears to produce an immunopathological catastrophe(3). DHF can occur during primary dengue infection in infants whose mothers are immune and probably carriers of non-neutralising antibodies against dengue(22). In many outbreaks such as one seen in Cuba in 1981, dengue shock syndrome was documented exclusively in children under 14 years of age. All such patients had a secondary rise of antibodies against dengue, indicating a previous infection with a closely related virus or another strain of dengue virus(23). Non-immune (unsensitized) subjects exposed to dengue virus even during outbreaks of DHF may present with the milder 'classical' dengue fever(24).

How a second dengue infection causes a severe disease and why only some patients get a severe disease is not understood. It has been postulated(25) that when antibody residua from first infection is able to neutralize a second virus type, second-

ary infection is mild. However, when no corss reactive neutralizing antibodies are present, the second infection is under influence of enhancing antibodies and the resulting disease is severe. It is also possible(26) that South East Asian dengue virus is inherently more capable of supporting severe antibody enhanced reaction.

Pathology

It is difficult to say about pathology in 'classical' dengue fever for want of sufficient pathologic material as it is hardly ever fatal. In DHF, pathological hemorrhages are seen in the upper gastrointestinal tract, interventricular septum of heart, on the pericardium and subserosal surfaces of major viscera. Focal hemorrhages are also seen in the lungs, liver, adrenals, and subarachnoid space. The liver is usually enlarged with fatty changes. Pleural effusions are present in most of the cases(24).

Microscopically, the pathognomonic lesion is in capillaries, with endothelial swelling, perivascular edema and infiltration with mononuclear cells(20).

Dengue virus is usually absent from the tissues at the time of death. Rarely, in infants less than one year of age who have died of 'primary' dengue infection, virus could be isolated from the liver and lymphatic tissues(24).

Pathogenesis of DHF

As mentioned earlier, DHF is seen when the subject is 'secondarily' infected with a heterologous dengue virus; the 'primary' infection having provided non-neutralizing antibodies of IgG type. It is postulated that the pre-existing antibodies and the infecting virus make immune complexes that attach readily to the mononuclear phagocytes and the complement system is activated. This results in release of vasoactive amines from the platelets. The blood clotting and fibrinolytic systems are activated, resulting in DIC like picture. This, associated with thrombocytopenia and liver damage, leads to multifocal hemorrhages. Capillary damage leads to leakage of fluid, electrolytes, plasma proteins and occasionally red blood cells to extracellular space. This internal redistribution of fluid together with decreased intake by the patient and vomiting results in hemoconcentration, hypovolemia, metabolic acidosis and hyponatremia(l).

Clinical Manifestations

The dengue viral infections *{Fig.* 2) may be asymptomatic, may present as 'classical' dengue fever or lead to 'dengue hemorrhagic fever' (DHF) with or without shock(17).

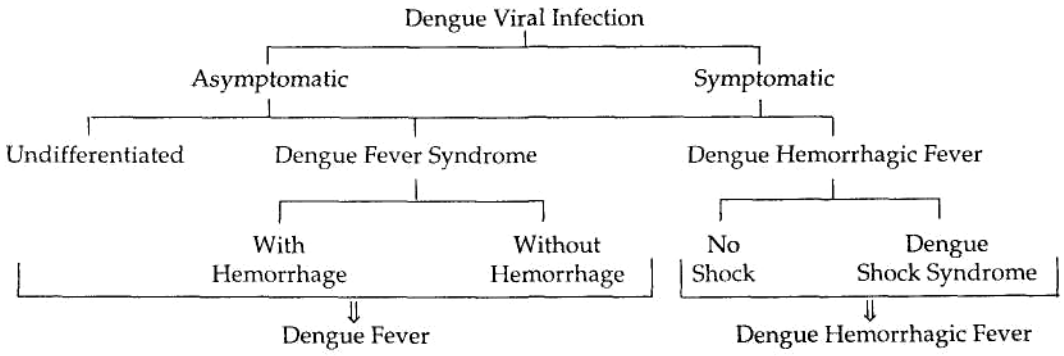

Fig. 2. Spectrum of dengue viral infection.

(a) *Dengue Fever*

Manifestations vary with age and from patient to patient. In infants and children, the disease may be undifferentiated and mimics upper respiratory infection. In dengue outbreaks, where older children are infected, classical syndrome characterised by biphasic fever, myalgia or arthralgia, rash, leukopenia and lymphadenopathy is seen.

The incubation period is 1 to 7 days after which there is onset of high grade fever. This lasts for about a week and is associated with severe bodyache, generalized lymphadenopathy, intense frontal/retrobulbar headache, vomiting, anorexia and occasionally cutaneous hyperaesthesias. There is a generalized 'transient' macular rash which blanches on pressure. This is followed by 1 or 2 days of defervescence when the body temperature falls to normal. There may be a second small rise in body temperature. This second rise in temperature is accompanied by the emergence of a generalized morbilliform, maculopapular rash which disappears in 1-5 days. There may be desquamation also. Hemorrhages, in the form of epistaxis, petechiae or purpuric lesions are uncommonly seen in 'classical' dengue fever(24). After the febrile stage, prolonged asthenia, depression, bradycardia and ventricular extrasystoles may occur, though infrequently.

(b) Dengu Hemorrhagic Fever

The incubation period and onset are similar to dengue fever, but within the next 2-3 days, there is a rapid deterioration and collapse. In this critical phase, the patient usually has cold clammy extremities, a warm trunk, flushed face, diaphoresis, restlessness, irritability and mid-epigastric pain. Frequently, there are scattered petechiae on the forehead and extremities; spontaneous ecchymosis may appear. Easy bruisability and bleeding at sites of venepuncture are also common. Fewer than 10% of patients would have gross ecchymosis or gastrointestinal bleeding, usually following a period of uncorrected shock(24). A macular or maculopapular rash may occur. Breathing is rapid and labored and there may be circumoral or peripheral cyanosis. The pulse is weak and rapid; heart sounds are faint. There is narrowing of pulse pressure (20 mm Hg or less). The liver may enlarge and is usually firm and tender. Untreated shock ends fatally within 12 to 24 hours.

The diagnostic criteria for DHF/ dengue shock syndrome (DSS) include thrombocytopenia (platelets < 1,00,000/cu mm) hemoconcentration (hematocrit > 20% of base line), hemorrhagic manifestations and/or hypotension(l). These criteria present certain practical problems. The base line hematocrit may not be known; it may already be low due to nutritional factors or the fall may be related to bleeding *per se*. In some of the reported studies(27), hemoconcentration has not been a consistent observation.

After 1-2 days of crisis, convalescence is fairly rapid in children who recover. Fever settles down. Bradycardia and extrasystoles are common in convalescence. Infrequently, there is a residual brain damage caused by prolonged shock or occasionally by intracranial hemorrhage. Other neurological manifestations such as seizures, spasticity, altered sensorium or presence of transient paresis have also been reported in dengue hemorrhagic fever, usually in association with Dengue 2 virus(28).

Dengue 3 viral infection has also been known to cause a stormy clinical syndrome characterized by encephalopathy, hypoglycemia, markedly elevated liver enzymes and occasionally jaundice(29).

Diagnosis

Etiological diagnosis in dengue viral infection can be made by serological studies or by isolation of the virus from blood leukocytes or serum. Serological diagnosis depends on a fourfold or greater rise in antibody titer in paired sera by the following tests(3): *(a)* Hemagglutination inhibition (HI) test; *(b)* Complement fixation; (c) Enzyme radio-immunoassay; and *(d)* Neutralization test.

For comparative studies of antibody titers, blood samples need to be taken during the febrile phase, preferably very early and later during the convalescent phase, *i.e.,* 3rd week after the onsert of fever. Antidengue IgM antibodies have a transient rise after dengue infections; antidengue IgG antibodies also show a rise. IgG antibodies may preexist in patients who have had sensitization due to previous dengue infection or in infants whose mothers have had infection.

It may not be possible to distinguish the infecting virus by serologic methods alone, particularly when there has been a prior infection with another member of flavivirus. In these cases, virus can be recovered from acute-phase serum after inoculating tissue culture or living mosquito. Viral RNA can be detected in blood or tissues by specific complementary DNA probes or amplified by the polymerase chain reaction [PCR](24).

Complement C_3 levels can be quantitated by SIRD technique(21); similarly, circulating immune complexes can be evaluated by many methods, including precipitation with polyethylene glycol. The laboratory abnormalities reported in literature are variable and it is not possible to lay down a consistent list of abnormalities.

Other Laboratory Tests

Pancytopenia may occur in the acute phase of dengue viral infection. Leukopenia (in range of 2000/cu mm) is seen in 'classical' dengue fever. Thrombocytopenia is universally seen in DHF. Also, in DHF during clinical shock, a rise in hematocrit (20% or more than baseline) is seen. Other hematological and biochemical abnormalities include prolonged bleeding time, decreased prothrombin levels (seldom to less than 40% of control), subnormal fibrinogen values, increased fibrin degradation products, consumption of complement, metabolic acidosis, hyponatremia, hypoproteinemia, hypochloremia and raised blood urea nitrogen. Serum levels of SGOT and SGPT are often elevated(28). Roentgenograms of the chest reveal pleural effusion in nearly all patients of DHF(24).

Differential Diagnosis

A large number of viral, rickettsial and bacterial infections besides malaria are considered in the differential diagnosis(20). Four arboviral diseases have dengue-like course but without rash - Colorado tick fever, Sand fly virus fever, Rift valley fever and Ross river fever(3). Other diseases having features quite indistinguishable from dengue are chikungunya, o'nyong-nyong and West Nile fever(24). A definite epidemiological and serological evidence is required for differentiation. Hemorrhagic manifestations may occur in meningococcemia, scrub typhus and leptospirosis. Some other viral hemorrhagic fevers which mimic dengue are Kaysanur Forest disease, Yellow fever, Lassa fever, and Hemorrhagic fever with renal syndrome(20).

Treatment

There is no specific antiviral treatment and the management is essentially supportive and symptomatic. Antipyretics and cold sponging are used for hyperpyrexia. Salicylates and NSAIDs should be avoided

for their effect on hemostasis; they may also result in metabolic acidosis.

The most important therapy is volume and electrolyte replacement(20,30). In dengue fever (DF), this can be achieved with ORS or fruit juices. A few patients of DF may require intravenous fluids. The volume and type of fluid is similar to that used in diarrhea with moderate isotonic dehydration.

The management of DHF/DSS includes administration of crystalloids by intravenous route. The following can be offered as broad guidelines for fluid administration to combat shock. Administer normal saline at 20 ml/Kg over 20-30 minutes. Monitor pulse, perfusion and blood pressure. If no responses is observed, repeat the infusion once. If even after 2 infusions, no response is observed, it is advisable to place a CVP line. Observe CVP for 10 minutes after fluid challenge. If it is elevated or normal, dopamine/dobutamine support may be needed to augment myocardial contractility. However, if the CVP is still decreased, further administration of normal saline in increments of 5-10 ml/kg over 20-30 min may be needed till CVP comes to normal. The response should be observed for at least 10 min following infusion. Increased capillary permeability in DSS may cause fluid leak in the tissues. The fluid requirement in DSS may therefore be higher as compared to other varieties of shock. Infusion should be continued at this rate till CVP persistently exceeds the initial value by 5 cm. Role of colloids in this phase is not very clear. In a child who is bleeding, blood administration may restore the hemodynamics faster(25). This should however be given only after 40-50 ml/Kg of saline has gone in. Due to capillary leak, colloids may cause obligatory water shift into the interstitial space. Acidosis and hypoglycemia, if present, should be managed appropriately.

There have been no randomized clinical trials to evaluate the role of platelet infusions in markedly thrombocytbpenic patients, with or without bleeding. Theoretically, it can be argued that antibodies would destroy even the transfused platelets. However, in children with massive bleeding, they still may have a place. It is difficult to give any definite recommendations regarding their use. Other modalities like high dose methylprednisolone(31) and intravenous immunoglobulins also remain controversial.

Other supportive measures include oxygen and non-hepatotoxic sedative like chloral hydrate (12.5 to 50 mg per kg subject to a maximum of 1 g). Infants may present with repeated convulsions associated with features of DHF/DSS. After initial correction of shock with volume replacement, and anticonvulsants, anticerebral edema measures such as intravenous frusamide may be needed.

There are occasional patients with renal failure after prolonged shock who need appropriate treatment. Dialysis is rarely needed. With careful monitoring of the patients and appropriate volume replacement as described, the mortality can be brought down considerably(30).

Prevention

Attenuated dengue viruses type 1,2,3 and 4 are under development in Thailand (6), but so far there is no satisfactory vaccine available. Therefore, prevention and control include breaking the transmission cycle of vector mosquitoes or by holding the mosquito population at extremely low levels. This involves avoiding mosquito bites by use of insecticides, covering the body with clothing, screening of houses and destruction of *Aedes aegypti* breeding

sites The water coolers should be cleaned once a week The overhead and other water storage tanks should be covered with tight fitting lids All water containers should be emptied daily before refilling and they should be kept covered Unused/broken bottles, cups, pots, tyres and other receptacles that can hold water should be disposed(17) A larvicide such as Abate, available as 1% sand granule formation and effective at a concentration of 1 ppm may be safely added to drinking water Adulticides like melathione may be sprayed during an epidemic(32).

Aedes aegyph being a day time mosquito, it is not practical to use insect repellants Also, most of the commercially available repellants contain DEET (N-N diethylmetoluamide) which at high concentrations (30% or more) could be toxic to infants and young children Mosquito coils or mats using pyrethrum derivates also are not entirely safe for children(33) Keeping the above in mind, a clean environment appears to be the only solution to the problem.

The WHO global control programme recommends the following broad guidelines for the dengue endemic countries (i) Selective integrated vector control with community and inter-sectoral participation, (n) Active surveillance based on a strong health information system, (in) Emergency preparedness, *(iv)* Capacity building and training, and *(v)* Research on vector control(6).

Prognosis

Classical dengue fever is a benign self-limiting disease and the only complications seen in childhood include fluid and electrolyte losses, hyperpyrexia and febrile convulsions Dengue hemorrhagic fever, on the other hand, is a serious illness, often fatal, unless early and intense management is instituted The overall reported case fatality in the recent epidemic of dengue in Delhi was m the range of 5% (34) although case fatality rate in Dengue hemorrhagic fever studied separately was 20-35% A better case management is likely to reduce the mortality

Entomologists and virologists(21) feel that the children would be the most susceptible hosts for the rapid and successive transmission of the dengue virus in the future epidemics.

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