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DENGUE FEVER IN TRAVELLERS: AN INCREASING PROBLEM

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The first clinical report of dengue fever (then referred to as break-bone fever) is attributed to Benjamin Rush in 1789. Its viral aetiology was only established during the first two decades of this century. During World War II, Sabin discovered the existence of more than one serotype and, during the investigation of a dengue outbreak in the Philippines in 1956, serotypes 3 and 4 of the dengue virus were identified. All four serotypes produce an identical disease.

The classical syndrome of dengue comprises fever, a rash, muscle and joint pains. A severe form of the disease with haemorrhagic manifestations (dengue haemorrhagic fever, DHF) was described as a separate clinical entity in the early 1950s.

EPIDEMIOLOGY

Dengue virus is an arbovirus of the flavi virus family, which also includes yellow fever virus and Japanese encephalitis virus. Dengue is spread by mosquitoes, mainly *Aedes aegypti* and *A. albopictus*, which are active during daytime. Currently, *A. aegypti* is found almost everywhere in the tropics between 30° North and 20° South latitudes, a geographical area in which nearly half of the world's population live. Dengue fever may be found in tropical and subtropical areas of Asia, Africa and America. In addition to humans, apes are considered to be the only other animal reservoir for dengue virus; neutralising antibodies against dengue has been found in these primates from Asia as well as from Africa. Replication of the virus within the mosquito takes 1-2 weeks and it is only then that this vector can transmit the virus.

A. aegypti has a short flight range, and thus dispersal of dengue viruses is almost entirely due to the movement of virally-infected persons; thus in the course of epidemics, dengue usually spreads along major transportation routes. Typically the spread of this infection exhibits the epidemiological features of an air-borne respiratory tract disease, and this transmission is intense and frequent in crowded, urban areas.

Dengue fever is endemic, and intermittently epidemic, in Asia and also in the Caribbean area. In 1981, the first epidemic of DHF occurred in Cuba and at least 10,000 cases of this severe form of the disease were reported. Epidemics usually occur during the rainy seasons when a high ambient temperature and an elevated humidity favour the proliferation of mosquito vectors.

Approximately 40 million cases of dengue fever have been calculated to occur annually worldwide. The Asian countries mainly involved are China, the Philippines, Vietnam, Thailand, Malaysia and Indonesia. In Latin America, a severe dengue epidemic which started in 1995 resulted in some 150,000 cases that year, including close to 4,000 of the severe haemorrhagic form.

Non-immune populations, especially children, support outbreaks of classical dengue fever. In certain areas where multiple dengue serotypes are endemic, outbreaks of

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DHF are also common. Case fatality rate may then reach five per cent but is usually lower.

An important observation in the Cuban outbreak in 1981 was that black children, although exposed to dengue type 1 and 2 infections, at the same or greater rates than white children, experienced DHF only one fifth to one tenth as often. This suggests that during secondary dengue infection, severity is modulated by the host's ethnicity and perhaps genetically determined herd immunity. This observation may also be supported by the fact that in Africa human dengue virus infections are unusually mild.

DENGUE FEVER AND TRAVELLERS

Statistics from the Swedish Institute for Disease Control demonstrate that South East Asia, and Thailand in particular, are the most common areas visited by Swedish travellers who present with symptoms of dengue fever during their stay or subsequently.[1] (Table 1.)

TABLE 1
Dengue virus infections diagnosed 1991-93 in Swedish travellers.[2]

	Area visited				
Total number of cases	Thailand	Other parts of South East Asia	Africa	South America	Not known
161	85 (52%)	53 (33%)	10	3	10

The number of diagnosed dengue cases in travellers has increased in recent years. During 1990 only 24 dengue cases were diagnosed in Sweden as compared to 161 cases in 1991-93.[2] Similar increases have also been noted in UK[3] and the US.[4] The use of more sensitive serological methods - the classical haemagglutination inhibition method has been replaced by one using immunofluorescence - may also account for the increased diagnostic rate. Occasionally DHF may also be seen in travellers[5] but surprisingly few cases of dengue have been diagnosed in Western Europe in spite of hundreds of thousands of such travellers to Asian countries annually.

Since dengue virus is spread by mosquitoes which are also active during daytime, the risk of exposure ought to be substantial for all travellers in endemic and epidemic areas. Recently I participated in a two weeks' journey in India and Bangladesh: in our group of 35 Scandinavian doctors, four of the party developed dengue fever symptoms on returning home. All four also were found to have an antibody titre rise. The remaining 31 travellers neither had any symptoms nor had any dengue antibodies in serum suggesting that subclinical dengue infections may be unusual in travellers.

Dengue fever has been on the increase worldwide in recent decades.[6] This is probably related to other global trends in population density, urbanisation, and climate. In the Pacific, non-climatic variables have not changed greatly since the 1970s, and dengue fever may have been mainly climate driven.[7] These findings suggest that dengue could be an increasing problem if the global climate continues to warm.

PATHOGENESIS

The primary infection with dengue virus, usually in early childhood, often results in a self-limiting febrile illness, which is followed by life-long immunity to that viral serotype.

After a few months of cross-protection against the three other serotypes, the child is again susceptible to infection with these. Available data suggest that haemorrhagic complications are associated with subsequent infection with a second serotype. This may explain the observation that foreign visitors who have not been exposed to dengue virus previously do not develop DHF during outbreaks of dengue fever as contrasted to the indigenous population who are being exposed to the virus for the second time round. It is usually believed that immune enhancement of virus replication underlies the development of severe haemorrhagic disease. Non-neutralising, cross-reacting antibodies opsonise virus of a second serotype and enhance uptake into mononuclear phagocytes, in which the dengue virus is known to replicate.[8]

Individuals who recover from the critical stage of DHF and shock do so very rapidly and without any sequelae. In those who die, there is usually no severe pathological manifestations in major organs and no evidence of secondary bacterial infection - implying an absence of immunosuppression. These observations suggest that physiologic dysfunction in DHF is related to biologic mediators that are capable of producing severe disease with only minimal structural injury. Release of inflammatory mediators by infected macrophages and activated lymphocytes, and activation of the complement system by antigen-antibody complexes are likely pathogenetic mechanisms that are involved in DHF.

A unique feature of dengue viruses that cause haemorrhagic fever in humans is their ability to activate both intrinsic anticoagulant and procoagulant systems simultaneously or sequentially. The clinical picture in the haemorrhagic form may depend on the degree to which each system is activated and the time at which such activation occurs. Since there is no animal model of DHF, only careful clinical studies in humans can clarify the background of this disorder. Human studies are complicated by rapid changes in the clinical picture and rapid clearance of potential biological mediators which make the interpretation of different reports on this matter rather difficult.[9]

CLINICAL MANIFESTATIONS

Manifestations may vary not only with age but also from patient to patient. In infants and young children the disease may have non-specific manifestations and is characterised by fever, rhinitis and mild cough. In outbreaks, a majority of infected older children and adults exhibit more severe symptoms. After an incubation period of 1-7 days, there is sudden onset of fever, which rapidly rises to 40°C or more, usually accompanied by headache. A transient, generalised, macular rash may appear. The pulse may be slow, relative to the degree of fever. Myalgia or arthralgia may occur soon after the onset and may be severe. Nausea and vomiting are apt to occur, and cutaneous hyperesthesia or hyperalgesia may develop. Somewhat later a second morbilliform, maculopapular rash appears. Rarely, oedema is noted on the palms and soles. About the time the second rash appears, the body temperature, which by then had returned to normal, may again become elevated, establishing a biphasic temperature curve.

The incubation period of DHF is presumed to be approximately that of dengue fever. A relatively mild first phase of abrupt onset of fever, malaise, vomiting, headache, anorexia and cough is followed after 2-5 days by rapid clinical deterioration and collapse. In this second phase the patient usually has cold extremities, a warm trunk, flushed face, diaphoresis, restlessness and irritability. Circumoral and peripheral cyanosis may also be found.

The four travellers to India/Bangladesh, including me, who contracted dengue fever had a high fever for 3-4 days, chills, pronounced myalgia and a measles-like exanthem. All had leucopenia, slight thrombocytopenia and raised aminotransferase levels in serum. One of the doctors experienced symptoms over a lengthier period, with difficulties of concentration and fatigue. Dengue may occasionally cause long-standing problems even in the absence of haemorrhagic disease. Depression is a well-known complication and when Rush described break-bone fever in 1789, it led another physician to suggest that he should change the name to 'breakheart fever'.[10]

The most common haematologic abnormalities during DHF with, or without, clinical shock symptoms, are a 20 per cent, or greater, increase in haematocrit value, thrombocytopenia, mild leukocytosis (seldom exceeding 10,000/mm^3), prolonged bleeding time, and moderately decreased prothrombin level. There may be elevation of the serum aminotransferases. Management requires immediate evaluation of vital signs and of the degree of haemoconcentration, dehydration and electrolyte imbalance. Close monitoring is essential.

SEROLOGY AND DIFFERENTIAL DIAGNOSIS

Blood for serological studies should be taken during the febrile period, preferably before the fourth or fifth day of illness, and a second sample should be obtained at least two weeks after onset. Serologic diagnosis depends on a fourfold or greater increase in antibody titre by the classical haemagglutination inhibition method, but an immunofluorescence technique is now often used. IgM antibody with dengue group specificity can be detected transiently (1-3 months) following both primary and secondary dengue infections.

The differential diagnosis includes a number of viral respiratory tract and influenza-like diseases as well as of malaria and leptospirosis. Four other arboviral diseases have dengue-like courses but without a rash: Colorado tick fever, sandfly fever, Rift Valley fever, and Ross River fever. Colorado tick fever occurs sporadically among campers and hunters in the western United States. Sandfly fever occurs mainly in the Mediterranean region, but also in the Middle East and parts of the Indian subcontinent. Rift Valley fever may be seen in most parts of Africa. Ross River fever is endemic in eastern Australia with an epidemic extension to Fiji.

TREATMENT

The only treatment in dengue fever is supportive. Bed rest is recommended during the febrile period. Antipyretic drugs or cold water sponging should be used to keep body temperature below high levels. Analgesics or mild sedation may be required to control pain. Because of its effects on haemostasis, aspirin should not be given.

DEVELOPMENT OF VACCINES

Recovery from dengue is accompanied by the development of neutralising antibodies. Available evidence indicates that immunity against other serotypes following dengue virus infection is brief, lasting 2-3 months at most. Resistance to the same serotype is life-long. However, epidemiologic studies indicate that individuals who have recovered from infection with one dengue serotype may develop DHF, with or without shock, if re-infected with another serotype. This severe illness appears to result from immune enhancement of viral replication, caused by the uptake by monocytes/macrophages of virus complexed to non-neutralising antibodies or to low-titre neutralising antibodies.

Alternatively, DHF may be caused by virulent dengue virus strains that have emerged during an epidemic episode.

It is of great importance to develop vaccines against dengue in a similar way as has been accomplished against other flavi viruses such as yellow fever and Japanese encephalitis virus. To produce a vaccine against dengue is, however, more complicated since it must give persistent protection against all four serotypes of this virus.

In discussing the prospects for live attenuated dengue vaccines, it should be kept in mind that there is no animal model for the disease. Laboratory markers could clearly differentiate parent virus from vaccine candidates, but human studies are the only certain method of determining attenuation. Small-scale clinical trials were carried out on individual serotypes for many years, most being acceptably attenuated, some not so. Dengue vaccine trials have recently been carried out successfully in Thailand, so live attenuated dengue vaccines are slowly becoming a reality.

Severe dengue disease has mainly been associated with antibodies from previous infections with other dengue serotypes. It remains to be determined if these cross-reactive dengue antibodies would form infectious immune complexes with an attenuated vaccine, which in turn would possibly revert to virulence through an increased efficiency of infection or through processing of the infectious immune complex by the infected cell. Neutralising and enhancing antibody titres must be carefully monitored in vaccinated populations to assess the consequences of waning protective antibodies from attenuated vaccines. The necessity for booster doses of the vaccines must be kept in mind.[11]

In spite of all these difficulties, several groups are currently working with dengue vaccine candidates and hopefully, by the turn of the century, travellers may go to South East Asia or Latin America protected against all four serotypes of dengue virus. Until then we have to rely on protection procedures against the mosquitoes, not an easy task since the small tormentors are active day and night.

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