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Review Article

Current Concept on Dengue: A Review

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Abstract: Dengue is a self-limited, systemic viral infection which is transmitted between humans by mosquitoes. The rapidly expanding global footprint of dengue is not only a public health challenge but also an economic burden. This review highlights the current understanding of dengue, including its pathogenesis, clinical manifestations, investigations that are used to diagnosis, management and prevention..
Keywords: Dengue, Aedes mosquitoes, Pathogenesis.

INTRODUCTION

Dengue Pandemic

The burden of dengue is large; an estimated 55 million infections per year occur across approximately 100 countries [1]. The primary vector, Aedes aegypti mosquito, has become widely distributed across tropical and subtropical latitudes. It emerged from Africa in the 15th centuries, spread into Asia through commercial exchanges in the 18th and 19th centuries. It has spread globally with the advent of increased travel and trade in the past 50 years [2]. In last few years the geographic range of a secondary vector, A. albopictus, has dramatically expanded [3]. Globalization of trade of tires from used vehicles, is thought to explain the dispersal of eggs and immature forms of these arboviral vectors into new areas [4]. Endemicity has also been facilitated by rapid urbanization in Asia and Latin America, resulting in increased population density with an abundance of vector-breeding sites within crowded urban communities.

Vector control, through chemical or biologic targeting of mosquitoes and removal of their breeding sites, is the mainstay of dengue prevention. Lack of long-term cross-immunity among the four virus types allows for multiple sequential infections.

The diagnosis should be considered in any patient presenting with fever that has developed within 14 days after even a brief trip to the tropics or subtropics, including those regions where dengue has not traditionally been considered an endemic disease [5, 6].

Virologic Features

Dengue is caused by one of four single-stranded, positive-sense RNA viruses of the genus flavivirus . Infectious virus and the virus-encoded NS1 are present in blood during the acute phase, and high-level early viremia and NS1 antigenemia have been associated with more severe clinical presentations [7-9]. The detection of NS1 is also the basis for commercial diagnostic assays [10].

Dengue viruses exist in two environments: the urban or endemic setting, where humans and mosquitoes are the only known hosts, and forested areas, where transmission of mosquito-borne viruses occurs between nonhuman primates [11]. Subtle antigenic differences exist between genotypes of the same serotype [12, 13]. But these may not be clinically relevant, since human infection with one serotype is believed to confer long-lived serotype-specific immunity. The dynamics of dengue viruses within urban and endemic populations are complex, involving the birth and death of viral lineages [14, 16]. Although dengue has emerged in multiple new territories over the past 50 years, the viruses themselves are paradoxically “local” in their evolutionary histories.

Immunopathogenesis

Epidemiologic studies have identified young age, female sex, high body-mass index are the risk factors for severe dengue. Virus strain, and genetic variants of the human major-histocompatibility-complex class I–related sequence B and phospholipase C epsilon 1 genes are also risk factors for severe dengue [18-21]. Secondary infection, in the form of two sequential infections by different serotypes, is also an

epidemiologic risk factor for severe disease [17, 22, 23]. Increased risk of secondary infection is thought to be linked with antibody-dependent enhancement of virus infection in Fc receptor–bearing cells and the generation of a large infected cell mass [24]. Large virus-infected cell mass promotes capillary permeability.

PATHOPHYSIOLOGY OF ENDOTHELIAL DYSFUNCTION

There is least evidence that the virus infects only endothelial cells. Minor nonspecific changes have been detected in histopathological studies of the microvasculature [25, 26]. Immunopathogenic events with definitive effects on microvascular permeability, thromboregulatory mechanisms lead to disruption in the function of the endothelial glycocalyx layer [27, 28]. This layer functions as a molecular sieve, selectively restricting molecules within plasma according to their size, charge, and shape. Hypoalbuminemia and proteinuria are observed during dengue infection due to crucial change in the filtration characteristics of the glycocalyx [29]. Both the virus and dengue NS1 are known to adhere to heparan sulfate, a key structural element of the glycocalyx, and increased urinary heparan sulfate excretion has been detected in children with severe infection [30, 31].

DIFFERENTIAL DIAGNOSIS AND DISEASE CLASSIFICATION

Most dengue virus infections are asymptomatic but a wide variety of clinical manifestations may occur, ranging from mild febrile illness to severe and fatal disease [1]. During the febrile phase, it may include other arboviral infections as well as measles, rubella, enterovirus infections, adenovirus infections, and influenza. Other differential diagnosis includes typhoid, malaria, leptospirosis, viral hepatitis, rickettsial diseases, and bacterial sepsis.

Previously four specific criteria, fever lasting 2 to 7 days, tendency to hemorrhage evidenced by a positive tourniquet test or spontaneous bleeding, a platelet count of less than 100×10^9 per liter, and evidence of a plasma leak based on changes in the hematocrit and pleural effusions are to be met to support a diagnosis of dengue hemorrhagic fever [32-34]. Recently World Health Organization (WHO) has revised dengue classification. Patients are now classified as having either dengue or severe dengue [1, 33, 35]. Patients who recover without any major complications are classified as having dengue. Severe dengue is diagnosed if the patients have any of the following conditions like plasma leakage resulting in shock, accumulation of serosal fluid sufficient to cause respiratory distress, or both; severe bleeding; and severe organ impairment.

CLINICAL MANIFESTATIONS

After an incubation period of 3 to 7 days, symptoms start suddenly and follow three phases — an initial febrile phase, a critical phase around the time of defervescence, and a spontaneous recovery phase.

Febrile Phase

The initial phase is typically characterized by high temperature (≥38.5°C) accompanied by headache, vomiting, myalgia, and joint pain, sometimes with a transient macular rash. Children have high fever but are generally less symptomatic than adults. Mild hemorrhagic manifestations such as petechiae. and bruising, particularly at venipuncture sites and a palpable liver are commonly noted. Laboratory findings include mild-to-moderate thrombocytopenia and leukopenia, often with a moderate elevation of hepatic aminotransferase levels. This phase lasts for 3 to 7 days, after which most patients recover without complications.

Critical Phase

In some patients, a systemic vascular leak syndrome becomes evident around the time of defervescence, characterized by increasing hemoconcentration, hypoproteinemia, pleural effusions, and ascites. Initially, physiological compensatory mechanisms are up-regulated in an attempt to maintain adequate circulation to critical organs. This result in narrowing of the pulse pressure. If the pulse pressure narrows to 20 mm Hg with signs of peripheral vascular collapse, dengue shock syndrome is diagnosed. Systolic pressure may remain normal or even elevated at this time, and the patient may appear deceptively well, but once hypotension develops, systolic pressure decreases rapidly and irreversible shock and death may follow despite aggressive attempts at resuscitation. During the transition from the febrile to the critical phase, the clinician must be aware of warning signs that clinically significant vascular leakage may be developing in the patient. The signs of impending deterioration include persistent vomiting, increasingly severe abdominal pain, tender hepatomegaly, increasing hematocrit level that is concurrent with a rapid decrease in the platelet count, serosal effusions, mucosal bleeding, and lethargy or restlessness.

Hemorrhagic manifestations are the most common during this critical period. In children, clinically significant bleeding are uncommon.. However, major skin bleeding, mucosal bleeding (gastrointestinal or vaginal), or both may occur in adults [36]. Moderate-to-severe thrombocytopenia is common, with platelet counts below 20×109 per liter often seen during the critical phase, followed by rapid improvement during the recovery phase. A transient increase in the activated partial-thromboplastin time and a decrease in fibrinogen levels are also frequently noted [37-39]. Rarely, other manifestations, including liver failure, myocarditis, and encephalopathy, can occur.

Recovery Phase

The increased vascular permeability is always short-lived, reverting spontaneously to a normal level after approximately 48 to 72 hours. This is concurrent with rapid improvement in the patient's symptoms. A second rash may appear during the recovery phase, ranging from a mild maculopapular rash to a severe, itchy lesion which suggests leukocytoclastic vasculitis. It resolves with desquamation over a period of 1 to 2 weeks.

DIAGNOSTIC TESTS

Dengue is diagnosed directly by detection of viral components in serum or indirectly by serologic means. The sensitivity of each method is influenced by the duration of the patient's illness [10]. During the febrile phase, detection of viral nucleic acid in serum by means of reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay or detection of the virus-expressed soluble nonstructural protein 1 (NS1) by means of enzyme-linked immunosorbent assay (ELISA) or the lateral-flow rapid test is sufficient for diagnosis. In persons, who have not been infected previously the diagnostic sensitivity of NS1 detection in the febrile phase can exceed 90%, and antigenemia may persist for several days after the resolution of fever [40-42]. The sensitivity of NS1 detection in the febrile phase is lower in secondary infections (60 to 80%), reflecting an anamnestic serologic response due to a previous dengue virus or related flavivirus infection [43].

Serologic diagnosis of dengue relies on the detection of high levels of serum IgM that bind dengue virus antigens in an ELISA or a lateral-flow rapid test. IgM can be detected as early as 4 days after the onset of fever. IgM seroconversion between paired samples is considered a confirmatory finding. Detection of IgM in a single specimen obtained from a patient with suspected dengue is widely used to establish a presumptive diagnosis. Commercially available IgM tests with good performance characteristics have recently been identified. In addition, patients with secondary infections with rapid anamnestic antibody responses in which dengue virus–reactive IgG may predominate over IgM. In clinical settings where methods of molecular detection (e.g., RT-PCR) are not available, investigation for elevated levels of dengue virus–reactive IgM or soluble NS1 in serum is a acceptable diagnostic approach in a patient in whom dengue is suspected [43, 45].

MANAGEMENT

At present no effective antiviral agents infection are available to treat dengue .Treatment remains supportive, with particular focus on careful fluid management. Patients, having no complications and able to tolerate oral fluids may remain at home with instructions to return to the hospital immediately if bleeding or signs suggestive of vascular leakage develop. Ideally it is better to evaluate these patients daily monitoring of complete blood count, hematocrit and platelet values.

If the patient develops dengue shock syndrome, prompt fluid resuscitation to restore plasma volume is vital, to maintain critical organ perfusion. Isotonic crystalloid solutions should be used, and isotonic colloid solutions should be reserved for patients presenting with profound shock or those who do not respond to initial crystalloid therapy [46]. To reduce the risk of the development of fluid overload, parenteral fluid therapy should be kept at optimum to maintain cardiovascular stability. Blood transfusion is lifesaving for patients with severe bleeding with compromised cardiovascular status. Platelet concentrates, fresh-frozen plasma, and cryoprecipitate may be given depending on the coagulation profile of patient. At present, there is no evidence that prophylactic platelet transfusions are beneficial in patients who do not have clinically significant bleeding, even with profound thrombocytopenia [47, 48]. In patients with severe dengue infection, adjuvant therapy, including vasopressor and inotropic therapies, renal-replacement therapy, and further treatment of organ impairment, may be necessary.

Recent trials have assessed chloroquine [49] oral prednisolone and balapiravir for treatment but, , there is no evidence available in favor of the use of any specific therapeutic agent for dengue.

EFFECTS ON HEALTH CARE SYSTEMS

The impact of dengue on health care systems is immense. Early identification of high-risk patients is important. Rapid and effective triage by experienced personnel at the primary health care level helps to reduce unnecessary admissions. Efficient and affordable transportation systems to facilitate daily clinical assessment, and public education campaigns to increase awareness of the disease all help to reduce hospital load. Among hospitalized patients, it is important to limit iatrogenic complications, including fluid overload. Ideally, patients with severe dengue infection should be treated in dedicated high-dependency units where frequent clinical observations can be made by experienced staff. Improvements in the early diagnosis and risk prediction of severe disease are very urgent, especially in areas with a high case burden. Ongoing research is going on to refine the WHO 2009 classification scheme, particularly with regard to warning signs for the development of severe disease.

NEW APPROACHES TO TARGETING THE VECTOR

New vector-control approaches by releasing genetically modified male mosquitoes that sterilize the wild-type female population. It reduces the egg output and the population size of the next generation that would be available for potential transmission of the dengue virus [50]. An alternative approach involves

embryonic introduction of strains of the obligate intracellular bacterium wolbachia into *A. aegypti*. Strikingly, wolbachia-infected *A. aegypti* are partially resistant to dengue virus infection [51, 52] and predicting the possibility of induction of widespread biologic resistance to dengue viruses [53].

Dengue vaccine, ChimeriVax (Sanofi Pasteur), is a tetravalent formulation of attenuated yellow fever 17D vaccine strains expressing the dengue virus prM and E proteins [54]. It was difficult to develop a vaccine for dengue which is safe and produce balanced neutralizing antibody responses to all four serotypes. Long-term follow-up of vaccines will be essential to understand whether waning vaccine-elicited immunity predisposes recipients to more severe outcomes on subsequent natural infection [55].

CONCLUSION

The research in field of dengue has been progressed over the past few decade which is aimed at producing a dengue vaccine. However, no vaccine can be full proof till date. Best efforts should be made to improve treatment through application of existing best practices in triage and fluid management, along with efforts to develop new antiviral or other therapeutic drugs .Simultaneously , new approaches to prevent transmission of the virus, such as through modification of mosquito populations, should be followed.

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