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Dengue: pathogenesis, prevention and treatment – A mini review

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Abstract:

Dengue is a threatening tropical disease which has become the cause of significant mortality, morbidity and economic burden. Dengue is an epidemic in over 100 countries, and it causes up to 25000 deaths every year. There is no specific cure available for the disease, hence fluid resuscitation is the only ultimate treatment given to patients in severe conditions. Dengue is more threatening in Southeast Asia, where it is the leading cause of deaths in children, and where all four serotypes of the dengue virus and the vector, *Aedes aegypti*, are endemic. In last few decades, an overwhelming increase was seen in dengue infections around the world and it is estimated that two fifths of the world's population is now at risk from dengue with the mortality rate of about 5%. To control dengue infection, combination of care measures are utilized which depends on the symptoms and severity of the fever, including oral rehydration solution or isotonic intravenous fluids and/or blood transfusions. Currently, the only effective way of preventing the dengue epidemics is eliminating the vector. This review covers pathogenesis, prevention and treatment of dengue infection.



Introduction

Dengue is an important tropical disease and has been reported in over 100 countries as epidemic, and approximately 2.5 billion people live in endemic conditions of the disease [1]. Dengue causes significant mortality, morbidity and economic burden in different regions across the world including Southeast Asia, Indian subcontinent and Oceania. In most of the countries, dengue epidemics occur during the warm, humid and rainy seasons, which favor abundant mosquito growth and shorten the extrinsic incubation period as well [2]. Dengue infection is considered one of the most important emerging viral diseases transmitted by mosquitoes to humans, in terms of both illness and death [3].

Majority of the infections caused by the dengue virus are asymptomatic [4]. The virus generally causes mild conditions known as Dengue Fever (DF), or a more severe conditions characterized by capillary leakage, known as Dengue Haemorrhagic Fever/Dengue Shock Syndrome (DHF/DSS) [5]. Shocks and plasma leakage from the capillaries are more common in children, whereas internal hemorrhage is frequently seen in adults [6]. In Asian countries children of age less than fifteen years are more severely affected than adults [7]. Whereas, in America the adult population is mostly affected but the severity of the disease is very low [8]. Any dengue serotype provides lifetime immunity to the infected person but the risk of developing a more severe form of the disease DHF/DSS is very high upon secondary infection with another serotype [9]. The reason behind this is most likely the cross reaction between antibodies [10], and memory T cells [11], which are thought to be directly involved in the pathophysiology of DHF/DSS.

Dengue virus is transmitted by the *Aedes aegypti*, which breeds in natural and artificial water containers [12]. The virus is single-stranded, positive-sense RNA virus of the family Flaviviridae and have four serotypes namely DENV type 1, DENV type 2, DENV type 3 and DENV type 4 [13]. These serotypes can be further classified into different genotypes on the basis of nucleotide variations. The genetic differences are usually associated with different level of infectivity and severity of the disease [14]. The mechanisms leading to differences in pathogenicity are being studied, but still no evidence has

been found. The high rate of mutations makes new genotypes, but the virulent genotype of serotype 2 (Southeast Asian) has been stably replicating since the 1940s [15]. Serotype-2 is mainly responsible for maximum of mortalities cause by dengue.

Methods

Literature search strategy and selection criteria

A systematic and comprehensive scientific review was compiled on dengue economic burden, pathogenesis, prevention and treatment. Literature search was carried out by using the terms, “dengue pathogenesis”, “dengue treatment”, and “dengue prevention”. Over 150 articles, published from 1978 to 2015, were accessed on Google Scholar and PubMed within the search criteria. Forty six well-reputed articles closely related to the subject of this review were included.

Discussion

Pathogenesis

People bitten by *Aedes aegypti* mosquito are diagnosed with high fever and severe joint pain that are the common symptoms of dengue fever [16]. Although dengue is a very old disease but recently an alarming increase has been seen in the geographic range, along with the severity of infection [17]. When an *Aedes aegypti* feeds on the human, it injects the virus into the blood stream. The virus targets the immature Langerhans cells and keratinocytes [18]. The Infected cells then migrate to lymph nodes, and the virus then attacks monocytes and macrophages. Consequently, the infection is replicated and virus migrates to various parts through the lymphatic system. The presence of the viruses in the blood stream is known as viremia. As a result of this viremia, many other cells get infected including blood-derived monocytes [19], myeloid dendritic cells [20], and splenic and liver macrophages [21]. Macrophages and lymphocytes are mainly infected with the virus [22]. Viremia occurs within two to six days of infection [10]. Studies have reported high level of viremia in DHF patients as compared to DF patients [23].

One of the characteristic features of DHF is plasma leakage into the abdominal and pleural cavities, while in DF there is no plasma leakage [24]. Plasma leakage in DHF causes low platelet counts [25] that is below 100,000/mm³ within 1–2 days of infection and it mainly

remains low for 3–5 days in most cases. The mean value of platelets in DSS cases is around 20,000/mm³, however in severe cases the platelet counts have frequently been seen below 50,000/mm³. Bleeding is commonly observed in both DHF and DF. Hemorrhages are also frequently seen in skin, subcutaneous tissues, liver and heart [26]. Liver is frequently affected But severe damage is not very common [27,28]. Elevated liver enzymes are commonly observed in both DF and DHF but are more severe in later [24].

In vitro studies on dengue virus have shown that all serotypes can replicate in epithelial cells [29]. However, epithelial cells from different tissues possess different activation patterns [30]. Dengue infection in the epithelial cells often causes functional damage without changing the morphology of the cells [28]. Biopsy specimens from skin have shown that mainly the capillaries located in the dermal papillae are affected [28]. Microvascular permeability has been reported in both the cases of DHF and DSS [31]. Several reports on dengue pathogenesis have confirmed that vascular damage as the central characteristic of both DHF and DSS [32]. Presence of dengue antigens have been reported in different cell types including monocytes, alveolar macrophages, splenic lymphocytes, peripheral blood, and endothelial cells of liver and lungs [22]. Bone marrow stromal cells are also susceptible to dengue virus [33]. Autopsy samples of infected people have demonstrated the presence of dengue virus in kidney [34], and even in brain [35].

Impact of the Disease

Every year dengue infects between 50 to 100 million people worldwide [36], causing up to 25,000 deaths [37]. According to World Health Organization (WHO) [34], dengue infections increased by three fold between 1960 and 2010. Many factors could have contributed to this increase of dengue infections, including population growth, urbanization, and global warming. The increase in dengue incidence worldwide, and absence of specific drugs for treating the disease make it an overwhelming health issue [38].

Dengue is more threatening in Southeast Asia, where it is the leading cause of deaths in children [3], and where all four serotypes of the dengue virus and the vector, the *Aedes aegypti* mosquito, are endemic. In few decades an overwhelming increase was seen in dengue infections

around the world and it is estimated that two fifths of the world's population is now at risk from dengue with the mortality rate of about 5% [1].

Treatment

Currently, no specific and effective treatments are available for the dengue. For the alleviation of symptoms and prevention of shocks, fluid resuscitation with colloid or crystalloid solutions is administered [39]. Sometimes, combination of care measures are utilized which depends on the symptoms and severity of the fever, including oral rehydration solution or isotonic intravenous fluids and/or blood transfusions. Plasma leakage in DF is self-limiting and lasts for 48 hours, so shocks can be prevented by replenishing the plasma immediately; however, excessive fluid treatments result in serious complications including respiratory failure and pulmonary oedema [40]. Some reports suggest crystalloid fluids are more effective in controlling dengue complications [41]. Sometimes corticosteroids are also used, in addition to fluid replacement. They are thought to be effective for stabilizing capillary permeability [42].

Conclusion

At present, controlling the dengue mosquito is the only available method, for preventing the epidemics. However, more research on the development and evaluation of vector control tools and strategies is needed [43]. In conclusion, current research trends on the prevention and treatment of dengue include different means of vector control, vaccine development, and novel antiviral drugs [44].

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