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Assessment of different factors responsible for the prevalence of dengue in Jawaharlal Nehru medical college and hospital, Bhagalpur, Bihar

Dr. Shreya[1], Dr. MN Jha[2*], Dr. Obaid Ali[3]

[1] Junior Resident, Department of Internal Medicine, Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar, India.
[2] Associate Professor, Department of Internal Medicine, Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar, India
[3] Assistant Professor, Department of Internal Medicine, Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar, India
[*] Corresponding Author: Dr. MN Jha

Abstract
India is one of the seven identified countries in the South-East Asia region regularly reporting incidence of DF/DHF outbreaks and may soon transform into a major niche for dengue infection in the near future. The first confirmed report of dengue infection in India dates back to 1940s, and since then more and more new states have been reporting the disease which mostly strikes in epidemic proportions often inflicting heavy morbidity and mortality, in both urban and rural environments. Hence based on the above findings the present study was planned for Assessment of Different Factors Responsible for the Prevalence of Dengue in Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar.

The present study was planned in Department of Internal Medicine, Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar, India. Total 50 cases of the dengue diagnosed were enrolled and evaluated in the present study. All probable cases that had high grade fever, lymphadenopathy, hepatomegaly, features of shock or haemorrhage, and so forth and were admitted with provisional diagnosis of dengue fever.

The data generated from the present study concluded that Dengue fever cannot just be simply considered as a viral infection, especially in a scenario where so many atypical presentations are seen. There are so many aspects which are manifested differently which when noticed promptly can help in reducing complications of DHF and DSS. Lastly use of mosquito control measures should not be underestimated because it forms the baseline of the treatment in in urban as well as rural population. Early diagnosis and careful management with proper fluid administration will help in reducing the mortality associated with dengue shock syndrome and haemorrhagic fever. Platelet transfusions has a little role in the management of dengue patients.

Keywords: Dengue, Mosquito, Fever, etc

Introduction

Dengue is the most common and important arthropod-borne viral (arboviral) illness in humans. It is transmitted by mosquitoes of the genus Aedes, which are widely distributed in subtropical and tropical areas of the world (see the image below). The incidence of dengue has increased dramatically in recent decades, with estimates of 40%-50% of the world's population at risk for the disease in tropical, subtropical, and, most recently, more temperate areas [1].

A small percentage of persons who have previously been infected by one dengue serotype develop bleeding and endothelial leak upon infection with another dengue serotype. This syndrome is termed severe dengue (also known as dengue hemorrhagic fever and dengue shock syndrome).

Dengue fever is typically a self-limited disease with a mortality rate of less than 1% when detected early and with access to proper medical care. When treated, severe dengue has a mortality rate of 2%-5%, but, when left untreated, the mortality rate is as high as 20%.

Many individuals with dengue may be asymptomatic. Many patients with dengue experience a prodrome of chills; rash, including erythematous mottling of the skin; and facial flushing, which may last 2-3 days. Children younger than 15 years who have dengue usually have a nonspecific febrile syndrome, which may be accompanied by a maculopapular rash. Dengue should be suspected in individuals who present with high fever (104°F/40°C), retro-orbital headache, muscle and joint pain, nausea, lymphadenopathy, vomiting, and rash and who have traveled within 2 weeks of symptom onset to an area where appropriate vectors are present and dengue transmission may be occurring.

The initial phase of severe dengue is similar to that of dengue fever and other febrile viral illnesses. Shortly after the fever breaks (3-7 days after symptom onset or sometimes within 24 hours before), signs of plasma leakage appear, along with the development of hemorrhagic symptoms such as bleeding from sites of trauma, gastrointestinal bleeding, and hematuria. Patients may also present with severe abdominal pain, persistent vomiting that may contain blood, fatigue, and febrile seizures (in children).

The subsequent 24 hours frequently prove critical. If left untreated, hemorrhagic fever most likely progresses to shock. Common symptoms in impending shock include abdominal pain, vomiting, and restlessness. Patients also may have symptoms related to circulatory failure, such as pallor, tachypnea, tachycardia, dizziness/lightheadedness, and a decreased level of consciousness.

Dengue is the most common and important arthropod-borne viral (arboviral) illness in humans. Globally, 2.5-3 billion individuals live in approximately 112 countries that

experience dengue transmission. While the annual incidence is unclear owing to incomplete global reporting and misclassification of illness, approximately 3.2 million individuals were infected globally in 2015. It is caused by infection with 1 of the 4 serotypes of dengue virus, which is a Flavivirus (a genus of single-stranded nonsegmented RNA viruses). Infection with one dengue serotype confers lifelong homotypic immunity to that serotype and a brief period (approximately 2 years) of partial heterotypic immunity to other serotypes, but an individual can eventually be infected by all 4 serotypes. Several serotypes can be in circulation during an epidemic.

Dengue is transmitted by mosquitoes of the genus Aedes, which are widely distributed in subtropical and tropical areas of the world (see the image below). An individual with dengue is capable of transmitting the virus for 4-5 days (maximum, 12 days) to a capable vector. After an incubation period of 5-10 days, the infected mosquito can transmit virus for the rest of its life span (2 weeks to 1 month). Aedes albopictus is more cold tolerant than Aedes aegypti, so it can survive and transmit virus in the more temperate regions of the United States and Europe.

The global incidence of dengue has increased dramatically in the last several decades, with an estimated 40%-50% of the world's population in 128 countries at risk [2, 3, 4]. Today, severe dengue largely affects Asian and Latin American countries, where it is a leading cause of hospitalization and death. The World Health Organization (WHO) ranked dengue as one of the top ten threats to global health in 2019 [5].

Initial dengue infection may be asymptomatic (50%-90%) [6], may result in a nonspecific febrile illness, or may produce the symptom complex of classic dengue fever (DF). Classic dengue fever is marked by rapid onset of high fever, headache, retro-orbital pain, diffuse body pain (both muscle and bone), weakness, vomiting, sore throat, altered taste sensation, and a centrifugal maculopapular rash, among other manifestations. The severity of the pain led to the term breakbone fever to describe dengue.

A small percentage of persons who have previously been infected by one dengue serotype develop bleeding and endothelial leak upon infection with another dengue serotype. This syndrome is termed severe dengue (reclassified in 2009 by the WHO, previously referred to as dengue hemorrhagic fever and dengue shock syndrome).

Severe dengue has also been termed dengue vasculopathy. Vascular leakage in these patients results in hemoconcentration and serous effusions and can lead to circulatory collapse. This, in conjunction with severe hemorrhagic complications, can lead to a shock syndrome, which poses a greater fatality risk than bleeding per se [7].

Dengue virus transmission follows 2 general patterns: epidemic dengue and hyperendemic dengue. Epidemic dengue transmission occurs when dengue virus is introduced into a region as an isolated event that involves a single viral strain. If the number of vectors and susceptible pediatric and adult hosts is sufficient, explosive transmission can occur, with an infection incidence of 25-50%. Mosquito-control efforts, changes in weather, and herd immunity contribute to the control of these epidemics. Transmission appears to begin in urban centers and then spreads to the rest of the country [8]. This is the current pattern of transmission in parts of Africa and South America, areas of Asia where the virus has reemerged, and small island nations. Travelers to these areas are at increased risk of acquiring dengue during these periods of epidemic transmission.

Hyperendemic dengue transmission is characterized by the continuous circulation of multiple viral serotypes in an area where a large pool of susceptible hosts and a competent vector (with or without seasonal variation) are constantly present. This is the predominant pattern of global transmission. In areas of hyperendemic dengue, antibody prevalence increases with age, and most adults are immune. Hyperendemic transmission appears to be a major risk for dengue hemorrhagic fever. Travelers to these areas are more likely to be infected than are travelers to areas that experience only epidemic transmission [9].

Because the signs and symptoms of dengue fever are nonspecific, attempting laboratory confirmation of dengue infection by serodiagnosis, reverse-transcriptase polymerase chain reaction (RT-PCR), or culture is important. Serodiagnosis is made on the basis of a rise in antibody titer in paired IgG or IgM specimens. Results vary depending on whether the infection is primary or secondary (see Presentation and Workup). Dengue is a reportable disease in the United States; known or suspected cases should be reported to public health authorities.

Dengue fever is usually a self-limited illness. Supportive care with analgesics, judicious fluid replacement, and bed rest is usually sufficient. Successful management of severe dengue requires intravascular volume replacement, with careful attention to fluid management and proactive treatment of hemorrhage. Admission to an intensive care unit is indicated for patients with severe dengue.

Dengue fever is a mosquito-borne viral disease caused by 1 of 4 closely related but antigenically distinct serotypes of dengue virus, serotypes DENV-1 through DEN-4 [10]. Infection with one dengue serotype confers lifelong homotypic immunity and a brief period of partial heterotypic immunity (2 years), but each individual can eventually be infected by all 4 serotypes. Several serotypes can be in circulation during an epidemic.

Dengue viruses are transmitted by the bite of an infected female Aedes (subgenus Stegomyia) mosquito [11]. Both males and females require nectar for energy. Females require a blood meal as a source of appropriate protein for egg development. Globally, Aedes aegypti is the predominant highly efficient mosquito vector for dengue infection, but the Asian tiger mosquito, Aedes albopictus, and other Aedes species can also transmit dengue with varying degrees of efficiency.

Aedes mosquito species have adapted well to human habitation, often breeding around dwellings in small amounts of stagnant water found in old tires or other small containers discarded by humans. Even a bottle cap filled with water can serve as to incubate and hatch Aedes eggs. Eggs can survive periods of drying and will hatch when exposed to water. Humans are the preferred hosts.

Female Aedes mosquitoes are daytime feeders. They inflict an innocuous bite, usually on the back of the neck and the ankles, and are easily disturbed during a blood meal, causing them to move on to finish a meal on another individual, making them efficient vectors. Not uncommonly, entire families develop infection within a 24- to 36-hour period, presumably from the bites of a single infected mosquito.

Humans serve as the primary reservoir for dengue. Certain nonhuman primates in Africa and Asia also serve as hosts

but do not develop dengue hemorrhagic fever. Mosquitoes acquire the virus when they feed on a carrier of the virus. Persons with dengue viruses in their blood can transmit the viruses to the mosquito 1 day before the onset of the febrile period. The patient usually remains infectious for the subsequent 4-5 days (up to 12 days).

The mosquito can transmit dengue if it immediately bites another host. In addition, transmission occurs after 8-12 days of viral replication in the mosquito's salivary glands (extrinsic incubation period). The virus does not adversely affect the mosquito. The mosquito remains infected for the remainder of its life. The life span of A aegypti is usually 21 days but ranges from 15 to 65 days. Vertical transmission of dengue virus in mosquitoes has been documented [12]. The eggs of Aedes mosquitoes withstand long periods of desiccation, reportedly as long as 1 year, but are killed by temperatures of less than 10°C. Rare cases of vertical dengue transmission have been reported. In addition, rare reports of human-to-human transmission via needle-stick injuries have been published [13].

Once inoculated into a human host, dengue has an incubation period of 3-14 days (average 4-7 days) while viral replication takes place in target dendritic cells. Infection of target cells, primarily those of the reticuloendothelial system, such as dendritic cells, macrophages, hepatocytes, and endothelial cells, result in the production of immune mediators that serve to shape the quantity, type, and duration of cellular and humoral immune response to both the initial and subsequent virus infections.

Dengue viral infections frequently are not apparent. In most cases, especially in children younger than 15 years, the patient is asymptomatic or has a mild undifferentiated febrile illness lasting 5-7 days. Classic dengue fever primarily occurs in nonimmune, nonindigenous adults and children and is typically self-limiting. Recovery is usually complete by 7-10 days. Severe dengue (dengue hemorrhagic fever/dengue shock syndrome) usually occur around the third to seventh day of illness during a second dengue infection in persons with preexisting actively or passively (maternally) acquired immunity to a heterologous dengue virus serotype.

Dengue presents in a nonspecific manner similarly to that of many other viral and bacterial illnesses. Fever typically begins on the third day of illness and persists 5-7 days, abating with the cessation of viremia. Fever may reach 41C°. Occasionally, and more frequently in children, the fever abates for a day and recurs, a pattern that is termed a saddleback fever; however, this pattern is more commonly seen in dengue hemorrhagic fever.

Leukopenia, lymphopenia near the end of the febrile phase, and thrombocytopenia are common findings in dengue fever and are believed to be caused by direct destructive actions of the virus on bone marrow precursor cells. The resulting active viral replication and cellular destruction in the bone marrow are believed to cause the bone pain. Approximately one third of patients with dengue fever may have mild hemorrhagic symptoms, including petechiae, gingival bleeding, and a positive tourniquet test (>20 petechiae in an area of 2.5 X 2.5 cm). Dengue fever is rarely fatal.

Severe dengue occurs less frequently than dengue fever but has a more dramatic clinical presentation. In most of Asia, where it first was described, severe dengue is primarily a disease of children. However, in the Americas, and more recently reported in Taiwan, severe dengue has an equal distribution in all ages.

Severe dengue typically begins with the initial manifestations of dengue fever. The acute febrile illness (temperatures ≤40°C), like that of dengue fever, lasts approximately 2-7 days. However, in persons with severe dengue, the fever reappears, giving a biphasic or saddleback fever curve.

Along with biphasic fever, patients with severe dengue have progressive thrombocytopenia, increasing hematocrit (20% absolute rise from baseline) and low albumin (signs of hemoconcentration preceding shock), more obvious hemorrhagic manifestations (>50% of patients have a positive tourniquet test), and progressive effusions (pleural or peritoneal). Lymphocytosis, often with atypical lymphocytes, commonly develops before defervescence or the onset of shock. Transaminase levels may be mildly elevated or present in the several thousands associated with hepatomegaly in those patients with acute hepatitis. Low fibrinogen and elevated fibrin split products are signs of disseminated intravascular coagulation. Severe metabolic acidosis and circulatory failure can occur.

The critical feature of severe dengue is plasma leakage. Plasma leakage is caused by increased capillary permeability and may manifest as hemoconcentration, as well as pleural effusion and ascites. Bleeding is caused by capillary fragility and thrombocytopenia and may manifest in various forms, ranging from petechial skin hemorrhages to life-threatening gastrointestinal bleeding.

Liver damage manifests as increases in levels of alanine aminotransferase and aspartate aminotransferase, low albumin levels, and deranged coagulation parameters (prothrombin time, partial thromboplastin time). In persons with fatal dengue hepatitis, infection was demonstrated in more than 90% of hepatocytes and Kupffer cells with minimal cytokine response (tumor necrosis factor [TNF]–alpha, interleukin [IL]–2). This is similar to that seen with fatal yellow fever and Ebola infections [15].

As the term implies, severe dengue shock is essentially dengue hemorrhagic fever with progression into circulatory failure, with ensuing hypotension, narrow pulse pressure (< 20 mm Hg), and, ultimately, shock and death if left untreated. Death may occur 8-24 hours after onset of signs of circulatory failure. The most common clinical findings in impending shock include hypothermia, abdominal pain, vomiting, and restlessness.

The immunopathology of severe dengue remains incompletely understood. Most patients who develop severe dengue have had prior infection with one or more dengue serotypes. When an individual is infected with another serotype (ie, secondary infection) and produces low levels of nonneutralizing antibodies, these antibodies, directed against 1 of 2 surface proteins (precursor membrane protein and envelope protein), when bound by macrophage and monocyte Fc receptors, have been proposed to fail to neutralize virus and instead form an antigen-antibody complex.

This results in increased viral entry into macrophages bearing IgG receptors, allowing unchecked viral replication with higher viral titers and increased cytokine production and complement activation, a phenomenon called antibody-dependent enhancement.

The affected macrophages release vasoactive mediators that increase vascular permeability, leading to vascular leakage, hypovolemia, and shock. This mechanism, along with

individual host and viral genome variations, plays an active role in pathogenesis. Infants born to mothers who have had dengue, as maternally derived dengue neutralizing IgGs wane, are also thought to be at risk for enhanced disease.

Some researchers suggest that T-cell immunopathology may play a role, with increased T-cell activation and apoptosis. Increased concentrations of interferon have been recorded 1-2 days following fever onset during symptomatic secondary dengue infections. The activation of cytokines, including TNF-alpha, TNF receptors, soluble CD8, and soluble IL-2 receptors, has been correlated with disease severity.

Cuban studies have shown that stored serum sample analysis demonstrated progressive loss of cross-reactive neutralizing antibodies to DENV-2 as the interval since DENV-1 infection increased [16]. In addition, certain dengue strains, particularly those of DENV-2, have been proposed to be more virulent, in part because more epidemics of dengue hemorrhagic fever have been associated with DENV-2 than with the other serotypes. DENV-2–activated platelets were phagocytized in large numbers when the platelet activation inhibitor prostacyclin was added.

Several recent studies have investigated the causes of thrombocytopenia in dengue. Laboratory and human studies have suggested a direct correlation between activation and depletion of platelets, with a sharp drop occurring on day 4 of fever. A high number of dengue virus genome copies have been found in these activated platelets. Increased binding of complement C3 and IgG have also been found on the surface of these platelets. In addition to platelet activation, dengue infection has been found to activate the intrinsic pathway of apoptosis, with increased surface phosphatidylserine exposure, mitochondrial depletion, and activation of caspase 3 and 9 [17].

Dengue infection is caused by dengue virus (DENV), which is a single-stranded RNA virus (approximately 11 kilobases long) with an icosahedral nucleocapsid and covered by a lipid envelope. The virus is in the family Flaviviridae, genus Flavivirus, and the type-specific virus is yellow fever.

The dengue virus has 4 related but antigenically distinct serotypes: DENV-1, DENV-2, DENV-3, and DENV-4. Genetic studies of sylvatic strains suggest that the 4 serotypes evolved from a common ancestor in primate populations approximately 1000 years ago and that all 4 separately emerged into a human urban transmission cycle 500 years ago in either Asia or Africa [18]. Albert Sabin speciated these viruses in 1944. Each serotype is known to have several different genotypes. Viral genotype and serotype, and the sequence of infection with different serotypes, appear to affect disease severity.

Living in endemic areas of the tropics (or warm, moist climates such as the southern United States) where the vector mosquito thrives is an important risk factor for infection [19]. Poorly planned urbanization combined with explosive global population growth brings the mosquito and the human host into close proximity. Increased air travel easily transports infectious diseases between populations.

India is one of the seven identified countries in the South-East Asia region regularly reporting incidence of DF/DHF outbreaks and may soon transform into a major niche for dengue infection in the near future. The first confirmed report of dengue infection in India dates back to 1940s, and since then more and more new states have been reporting the disease which mostly strikes in epidemic proportions often inflicting heavy morbidity and mortality, in both urban and rural environments. Hence based on the above findings the present study was planned for Assessment of Different Factors Responsible for the Prevalence of Dengue in Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar.

Methodology

The present study was planned in Department of Internal Medicine, Jawaharlal Nehru Medical College and Hospital, Bhagalpur, Bihar, India. Total 50 cases of the dengue diagnosed were enrolled and evaluated in the present study. All probable cases that had high grade fever, lymphadenopathy, hepatomegaly, features of shock or haemorrhage, and so forth and were admitted with provisional diagnosis of dengue fever.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Results & Discussion

Dengue is the most common arthropod borne viral infection in humans. Anually around 50-100 million individuals are infected [20]. The incidence has increased manifold in India due to urbanization and migration of population into urban areas. Dengue virus belongs to the family Flaviviridae, which has four serotypes and are spread by the bite of infected Aedes mosquitoes2. Infection with one serotype confers lifelong homotypic immunity to that serotype and a brief period of partial heterotypic immunity to other serotypes [21]. 72 Dengue infection may be asymptomatic initially(50- 90%), in the form of nonspecific febrile illness, or may produce the symptom complex of classic dengue fever(DF). Classic dengue fever is marked by rapid onset of high grade fever, headache, myalgias, retroorbital pain, weakness, vomiting, maculopapular rash, etc. [22] A small percentage of patients may present with bleeding manifestations in the form of bleeding gums, hematuria, hematemesis, malena. This syndrome is called dengue hemorrhagic fever (DHF).

True endemicity will be reached when the adult infection declines and only the new entrants into the population, that is, the children, are affected more by the disease [23]. The clinical profile of dengue revealed that fever was the most common presenting symptom. Similar studies in and around India have also substantiated fever as being the most common presenting symptom. Abdominal pain and vomiting were found to be present among the study population, which could be due to the liver injury caused by the dengue virus. It is imperative to keep in mind that other infections that cause fever and gastrointestinal symptoms such as typhoid, leptospirosis, enteroviral infections are common in India and may often lead to a delay in the diagnosis of dengue. Our study suggests that dengue in all its forms should be included in the differential diagnosis of patients with fever and gastrointestinal symptoms. This conclusion was also made from a study done in a tertiary care center in Pakistan [24].

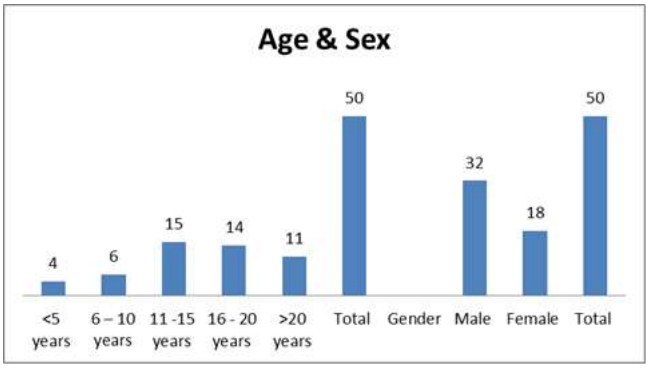

Fig 1: Demographic Details

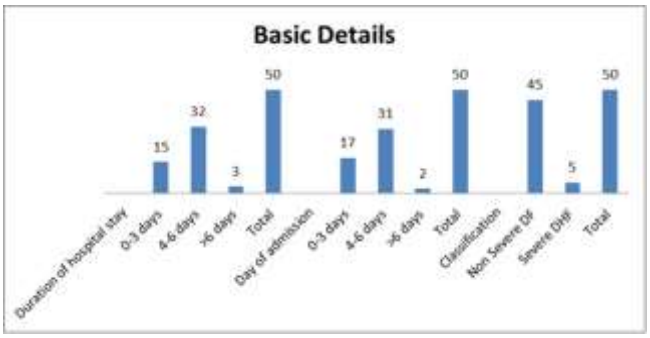

Fig 2: Basic Details

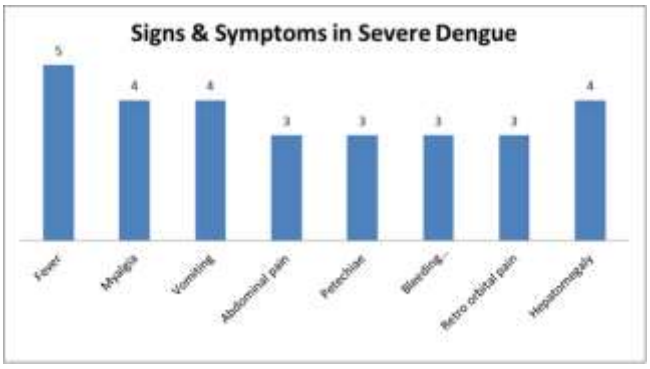

Fig 2: Signs & +symptoms in Severe Dengue Fever Cases

Table 1: Haemoglobin Count in No. of Cases

Hb in gm%	No. of Cases
<7	2
7.1 to 10	3
>10	45
Total	50

Table 2: Platelet count among the study population

Platelet count	No. of Cases
<20 x 10^3	1
20-50 x 10^3	16
50-100 x 10^3	10
>100 x 10^3	23
Total	50

During all these epidemics, children <15 years of age were quite severely affected, but majority of infection occurred in active adults in the age group of 16-60 years. Certain common signs and symptoms such as fever, headache, myalgia, arthralgia and bleeding manifestations have also been observed. However, few other studies have depicted differences in age and sex distribution and clin ical presentation [25].

Bleeding manifestations in the form of petechae, bleeding gums, hematuria, hematemesis and malena was observed in 7.5% of patients. Rajesh D *et al* have shown bleeding manifestations in 5.4% [26] and Laul A *et al* in 21% of patients [27]. Bleeding diathesis is a known feature of dengue because of low platelet count and leakage from blood vessels. Bone marrow suppression, immune mediated clearance and spontaneous aggregation of platelets to virus infected endothelium may be responsible for such thrombocytopenia.

The present study highlights the importance of dengue fever to clinicians in the areas of epidemiology, manifestations, complications and outcome of the disease. The study has the limitations inherent to a hospital record-based study, so meteorological and entomological data, information, education and communication (IEC) strategies and vector control measures initiated by the government are not correlated.

Dengue is emerging and serious public health problem worldwide. It is evident that the demographic characteristics and clinical profile of dengue infections have changed rapidly during the last three decades [28]. Increase in the number of dengue cases over the past few years has been attributed to rapid unplanned urbanization with unchecked construction activities and poor sanitation facilities contributing fertile breeding areas for mosquitoes and it is also seen that increase in the alertness among medical personnel following the epidemics and availability of diagnostic tools in the hospitals have contributed to the increased detection of cases [29].

In the recent few years, the world has seen varied clinical presentations of the dengue fever in different epidemics, even in the same regions and even in the same period of time. Where some known features are still manifesting, few atypical features are noted from several parts of the world as seen in our study. So a continuous sero-epidemiological surveillance and timely interventions are needed to identify the cases, so that its complications and mortality can be minimised.

Conclusion

The data generated from the present study concluded that Dengue fever cannot just be simply considered as a viral infection, especially in a scenario where so many atypical presentations are seen. There are so many aspects which are manifested differently which when noticed promptly can help in reducing complications of DHF and DSS. Lastly use of mosquito control measures should not be underestimated because it forms the baseline of the treatment in in urban as well as rural population. Early diagnosis and careful management with proper fluid administration will help in reducing the mortality associated with dengue shock syndrome and haemorrhagic fever. Platelet transfusions has a little role in the management of dengue patients.

References

1. World Health Organization. Dengue and severe dengue fact sheet. WHO. Available at http://www.who.int/mediacentre/factsheets/fs117/en/. April 2017; Accessed: September 28, 2017.
2. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, *et al*. The global distribution and burden of dengue. Nature. 2013 Apr 25. 496

(7446):504-7.
3. Brady OJ, Gething PW, Bhatt S, Messina JP, Brownstein JS, Hoen AG, *et al*. Refining the global spatial limits of dengue virus transmission by evidence-based consensus. PLoS Negl Trop Dis. 2012. 6 (8):e1760.
4. Wilson ME, Chen LH. Dengue: update on epidemiology. Curr Infect Dis Rep. 2015 Jan. 17 (1):457.
5. Ten threats to global health in 2019. World Health Organization. Available at https://www.who.int/emergencies/ten-threats-to-global-health-in-2019. 2019; Accessed: Feb 2, 2019.
6. Kyle JL, Harris E. Global spread and persistence of dengue. Annu Rev Microbiol. 2008. 62:71-92.
7. Statler J, Mammen M, Lyons A, Sun W. Sonographic findings of healthy volunteers infected with dengue virus. J Clin Ultrasound. 2008; 36(7):413-7.
8. Gubler DJ. Cities spawn epidemic dengue viruses. Nat Med. 2004 Feb. 10(2):129-30.
9. Wilder-Smith A, Gubler DJ. Geographic expansion of dengue: the impact of international travel. Med Clin North Am. 2008 Nov. 92(6):1377-90, x.
10. CDC. Imported dengue--United States, 1997 and 1998. MMWR Morb Mortal Wkly Rep. 2000 Mar 31. 49(12):248-53.
11. Engelthaler DM, Fink TM, Levy CE, Leslie MJ. The reemergence of Aedes aegypti in Arizona. Emerg Infect Dis. 1997; 3(2):241-2.
12. Chye JK, Lim CT, Ng KB, *et al*. Vertical transmission of dengue. Clin Infect Dis. 1997 Dec. 25(6):1374-7.
13. Wagner D, de With K, Huzly D, Hufert F, Weidmann M, Breisinger S, *et al*. Nosocomial acquisition of dengue. Emerg Infect Dis. 2004; 10(10):1872-3.
14. Rothman AL. Dengue: defining protective versus pathologic immunity. J Clin Invest. 2004 Apr. 113(7):946-51.
15. de Macedo FC, Nicol AF, Cooper LD, Yearsley M, Pires AR, Nuovo GJ. Histologic, viral, and molecular correlates of dengue fever infection of the liver using highly sensitive immunohistochemistry. Diagn Mol Pathol. 2006 Dec. 15(4):223-8.
16. Guzman MG, Alvarez M, Rodriguez-Roche R, Bernardo L, Montes T, Vazquez S. Neutralizing antibodies after infection with dengue 1 virus. Emerg Infect Dis. 2007 Feb. 13(2):282-6.
17. Hottz ED, Oliveira MF, Nunes PC, Nogueira RM, Valls-de-Souza R, Da Poian AT, et al. Dengue induces platelet activation, mitochondrial dysfunction and cell death through mechanisms that involve DC-SIGN and caspases. J Thromb Haemost. 2013 May. 11 (5):951-62. [Medline].
18. Wang E, Ni H, Xu R, Barrett AD, Watowich SJ, Gubler DJ. Evolutionary relationships of endemic/epidemic and sylvatic dengue viruses. J Virol. 2000 Apr. 74(7):3227-34. [Medline].
19. Centers for Disease Control and Prevention Web site. CDC traveler's health page. Dengue. Available at http://www.cdc.gov/Dengue/travelOutbreaks/. Accessed: October 20, 2011.
20. Suzzane M S, Dengue Medscape.Retrieved 4/10/2014 from http:// emedicine. medscape .com/article/215840.
21. Engelthaler DM, FinkTM, Levy CE, Lesile MJ. The reemergence of Aedesaegypti in Arizona. Emerg Infect Dis 1997; 3:241-2.
22. CDC Imported dengue-United States, 1997 and 1998. Morb Mortal Wkly Rep. 2000; 49:248-5.
23. Kavitha R. Dengue fever: the rise and the establishment of a new disease in Kerala, India with special references to the capital, Thiruvananthapuram. J Acad Clin Microbiol 2007; 9:65-70.
24. Khan E, Siddiqui J, Shakoor S, Mehraj V, Jamil B, Hasan R. Dengue outbreak in Karachi, Pakistan, 2006: experience at a tertiary care center. Trans R Soc Trop Med Hyg 2007; 101:1114-9.
25. Agarwal R, Kapoor S, Nagar R, Misra A, Tandon R, Mathur A, et al. A clinical study of the patients with dengue hemorrhagic fever during the epidemic of 1996 at Lucknow, India. Southeast Asian J Trop Med Public Health 1999; 30:735-40.
26. Rajesh D, Ishaque Md, et al. Clinical and Laboratory Profile of Dengue Fever.et al J of Asso Phy of India Dec 2015; 63:30-32.
27. Laul A et al. Clinical profiles of dengue infection during an outbreak in Northern India.J Trop Med 2016; 3: 223-34.
28. Seema A, Singh V, Kumar S, et al. The Changing Clinical Spectrum of Dengue Feverin the 2009 Epidemic of North India: A Tertiary Teaching Hospital Based Study. J ClinDiagno Res 2012; 6:999-1002
29. Gubler DJ, Dengue and Dengue hemorrhagic fever. Clin Microbial Rev. 1998; 11:480-96.