Dengue: An Emerging Disease in Nepal

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ABSTRACT

Dengue is an acute infectious disease caused by dengue viruses and transmitted by the Aedes species of mosquito. The rapid global spread of the dengue virus into new areas has begun to attract more research attention. A series of dengue fever outbreaks in several districts of Nepal has been recently observed. The evidence of all four serotypes (DEN – 1 - 4) could be a consequence of a sudden resurgence of a more severe dengue disease in Nepal. Health care providers need to become familiar with the disease to prevent or control the possibility of future outbreaks. The clinical features, diagnosis, treatment, epidemiological patterns and challenges of dengue virus infection in Nepal will be discussed here.

Keywords: *Dengue, epidemiological patterns, Nepal*

INTRODUCTION

Dengue virus (DENV) is a mosquito-borne single stranded RNA virus that belongs to the genus Flavivirus, family Flaviviridae. It has four serotypes, DEN-1, DEN-2, DEN-3 and DEN-4, which are capable of causing dengue fever (DF). Over the past several years, dengue epidemics have been increasing remarkably, and have become a major public health problem, particularly in tropical and sub-tropical countries. The World Health Organization (WHO) has currently estimated that there may be 50 million dengue infections occurring each year in the world, and this endemic appears in more than a total of a 100 countries, in Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific. Amongst these, the Western Pacific and South East-Asia are the most seriously affected areas, which bear nearly 75 % of the current global burden of DENV infection.[1] In South Asia, several dengue outbreaks have been observed in India alone, over the past several years .[2,3] In Nepal, a dengue case was first reported in 2004.[4] Since then, DF has been found to be spreading rapidly across the country within a short period of time.[5,6,7] Although DENV infection is one of the emerging diseases in Nepal, healthcare providers are sometimes found to have incomplete knowledge of the disease. This review will discuss the clinical features, diagnosis, treatment, epidemiological patterns and challenges of DENV infection in Nepal.

CLINICAL FEATURES, LABORATORY DIAGNOSIS AND TREATMENT

The incubation period of DF ranges from 4 - 10 days.[1] Classical dengue fever is characterized by the sudden onset of fever, which usually lasts for 2 - 7 days, severe headache, retro-orbital pain and joint and muscular pain. DF is also refered to as the 'breakbone' disease due to its nature of severe joint and muscular pain. Complications often occur within two days after the fall in temperature. Epistaxis, bleeding of gums, passage of black stools, rashes (petechiae, maculopapular, bruises, etc.) and sub-conjunctival hemorrhage are indicators of increasing disease severity. A maculopapular rash usually appears 3 - 4 days after the onset of fever.

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The clinical features of dengue fever vary from mild to severe. A grading system for dengue infection has been established based on the clinical and laboratory findings, and is known as Dengue fever (DF) or Dengue hemorrhagic fever (DHF) grade I to IV.[8] DHF grade III and IV are also called Dengue Shock Syndrome (DSS).

Clinical findings alone are not sufficient to make an accurate diagnosis of DENV as several other infectious diseases may present with similar findings, which underscores the need for laboratory testing for the dengue confirmation. Leucopenia, thrombocytopenia, increased hematocrit and liver enzyme levels are common laboratory findings suggestive of DENV infection. Serological tests, such as rapid diagnostic test (RDT), Enzyme-linked immunosorbent assay (ELISA) are widely used. In Nepal, serological testing has been used as an important tool for diagnosis of suspected DENV infection during outbreaks.[4,5,6,7] Despite widespread use, these serological tests, however, cannot confirm DENV among febrile patients, due to low sensitivity and cross reactivity with other flavivirus infections (e.g. yellow fever, west Nile virus, Japanese encephalitis), which may lead to false positive results.[9] Viral isolation and detection of viral antigens or RNA in tissue or serum provides the most specific test result. Currently, these methods, however; are not commonly used in Nepal, due to the poor laboratory infrastructure.

There is no specific antiviral treatment for the DENV infection. Most patients recover without complication. Symptomatic treatment is the mainstay of the treatment. Rest, fluid balance, antipyretics such as paracetamol (avoiding non-steroidal anti-inflammatory agents) is the treatment of DF. Monitoring of blood pressure, platelet count, hematocrit and hemorrhagic manifestations are essential. Intravenous fluids should be provided guided by blood pressure, hematocrit level and urine output. It should, however, be noted that excessive or too rapid intravenous fluid can cause fluid overload resulting in respiratory distress and even pulmonary edema.

Although acute dengue infection generally is asymptomatic or mild, it may sometimes present with DHF/DSS. Sometimes it can be fatal, if prompt and appropriate supportive treatment is not undertaken. Treatment limitations have prompted efforts to develop a vaccine against DENV. Although much progress has been made towards vaccine development, safe and effective vaccine has yet to be commercially available in the market. It should, however, be available at an affordable cost for the developing world, where the disease is becoming acutely endemic.

TREND OF DENGUE FEVER IN NEPAL

Although DENV infections have been found in our neighboring country India over a long period of time, there was no documented dengue case in Nepal prior to 2004. For the first time, DENV was identified as a causative agent in a patient with acute febrile illness in 2004.[4] Thereafter, minor dengue outbreaks were confirmed in nine districts in 2006.[5,6,10] In addition to these, acute DENV infection has been reported in one more district from western Nepal during 2007 - 2008 study among febrile patients attending the local hospitals,[7] indicating that DENV is becoming one of the major emerging infectious diseases in Nepal. It is plausible to assume that DENV could have been introduced into Nepal from India, due to the open border between the two countries. This hypothesis is further supported with the finding of nucleotide sequences of the Nepalese dengue strain that have been described to be very similar to the dengue strains circulating in India.[11] During the 2006 outbreaks, all four dengue serotypes were found to be circulating in Nepal.[6] It is clear that subsequent infection with different strains may lead to a more severe disease among the patients. Taken together, a sudden resurge of severe dengue disease can be, therefore, assumed to occur in the near future.

THE FIRST MAJOR OUTBREAKS OF DENGUE FEVER IN NEPAL

For the first time, Nepal had experienced major outbreaks of DF in several districts in 2010, particularly in Chitwan and Rupendehi districts. A total of 264 DF cases from across the country were admitted to Sukraraj Tropical and Infectious Disease Hospital (STIDH), Kathmandu, between July and December (Figure 1).

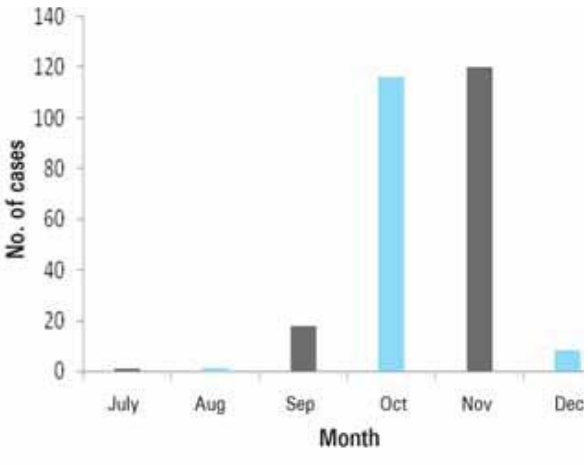

Figure 1. Monthly distribution of DF cases admitted to STIDH in 2010, Kathmandu, Nepal

There was one death reported due to DSS. The clinical features of these patients were consistent with the WHO definition of DF.[8] Of these, 31 % (81/264) of the patients were positive for both IgM and IgG immunoglobulins, using the rapid immunochromatograhic tests (Panbio Dengue Duo Cassette, Sinnamon Park Brisbane, Australia, or SD Bioline Dengue strip test, Standard Diagnostic Inc., Kyonggi-do, Korea), while 44 % (115/264) were IgM positive alone. However, serotypes responsible for the current outbreaks are yet to be identified.

Among the admitted DF cases, 63 % (168/264) showed thrombocytopenia (< 100,000/mm^3), of which 40 % (68/168) had a platelet count of less than 50,000/mm^3, mostly adults between the ages of 21 - 40 years (Figure 2), and 30 % (50/168) received a platelet rich plasma (PRP) transfusion during hospitalization. Increased liver enzymes levels were observed in 47 (65 %) of the 72 investigated patients. These results are in accordance with previous studies, where thrombocytopenia and elevated liver enzymes have been shown to be associated with DENV infection.[12,13]

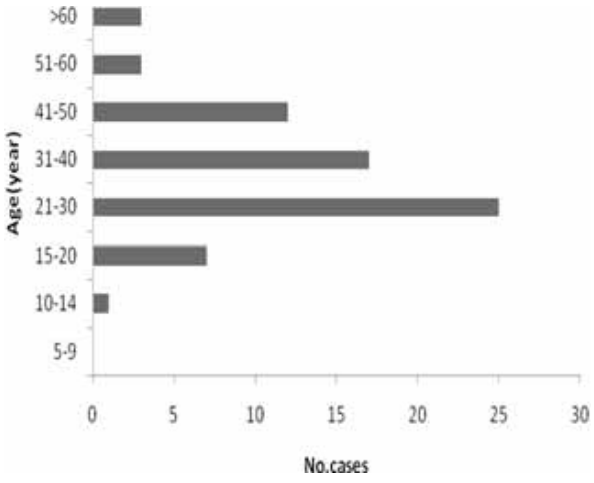

Figure 2. Age distribution of DF cases, having a platelet count < 50,000/mm^3

Of the total, 89 % (236/264) of cases were admitted between October and November. This finding is consistent with previous studies, in which increased dengue cases were observed after the rainy seasons in Nepal.[5,6,7,10] Nonetheless, it is not known whether dengue virus transmission is occurring in other seasons, because Nepal is geographically located in the sub-tropical area, and no comprehensive epidemiological study has been done year round.

Among the admitted DF cases, 95 % (253/264) were adults above 14 years of age (data not shown). A similar observation was made in a previous study.[7] 65 % of the cases were male (172/264). DF cases were reported in Kathmandu in 2006, either with a history of travel to India or with a history not known.[6,10] Nevertheless, for the first time, a DF case with no recent history of travel to a known dengue affected area was found in Kathmandu during the 2010 outbreaks. Therefore, it could conceivably be hypothesized that indigenous DENV might be circulating in Kathmandu, since, Ae. aegypti, the primary vector for the transmission of dengue virus, has already been reported in Kathmandu.[14]

CHALLENGES

Until 2006, DF was reported in nine districts (Figure 3), while Ae. aegypti, the primary vector of DENV transmission has been found in 5 districts.[10] During the 2010 outbreaks, DF cases were reported from 24 districts at STIDH alone, indicating that rapid geographical expansion is occurring within the country (Figure 4). This observation raises a serious concern about its potentiality to spread to other parts of the country. DF cases were also reported from the hilly regions above an altitude of 1000 meters, like in a previous study, where DENV infection (DEN-2) was confirmed from a hilly region (Dhading district) with a similar altitude.[6] Nevertheless, the vector responsible for these outbreaks has yet to be confirmed in those reported areas. It is suggested that the vector distribution is limited by the 10°C isothermal, and is relatively uncommon above an altitude of 1000 meters because of lower temperatures.[1] One study, however, has reported an outbreak of dengue fever at an altitude of 1,700 meters, with confirmation of the presence of the Aedes larva.[15] Hence, there is an urgent need for entomological surveillance beyond low land areas (southern plains districts), where the vector was thought to be confined previously. Aedes albopictu has been also associated with DENV transmission, and has been regularly reported in the southern plains districts .[10] Nonetheless, the role of Ae. albopictus in the transmission of DENV in Nepal is not very well documented, since its role has been shown to be relatively minor, compared to Ae. aegypti, in DENV transmission elsewhere.[16] So far, no accurate, reliable and timely information on DENV infection is available. To accomplish these requirements, a comprehensive nationwide integrated epidemiological-entomological surveillance needs to be put high on the priority, and must be incorporated into the national health policy.

Figure 3. Geographical distribution of dengue outbreaks, Nepal, 2006[10]

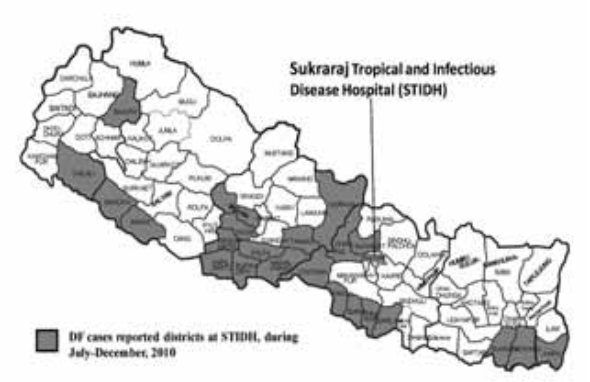

Figure 4. Geographical distribution of dengue cases admitted to STIDH, during July- December 2010, Kathmandu, Nepal

The presence of all four dengue serotypes (DEN – 1 - 4) in Nepal is a matter of serious concern and it may make dengue case management more complicated. In 2006, DEN-1 and DEN-3 were detected in patients living in Kathmandu, while DEN-2 and DEN-4 were detected in Dhading and Parsa districts respectively.[6] The existence of vector Ae. Aegypti, with multiple serotypes circulating in Kathmandu, may lead to a national health crisis since the city is densely populated and health care facilities are not well prepared to tackle possible future outbreaks. The occurrence of serotypes varying from place to place have been shown previously, while, serotypes responsible for the 2010 outbreaks, in several locations across the country, are yet to be known. Rapid and accurate identification of the infecting dengue virus serotype is not possible without molecular techniques. Polymerase chain reaction (PCR) offers a rapid and reliable method for identifying serotypes. Until the present, diagnosis of dengue in Neapl is based on clinical signs and a positive serological test. Hence, the national reference laboratory should acquire PCR techniques in order to reduce the need to send samples abroad for serotyping/genotyping and to get faster and more reliable test results locally. Such methods would also be useful in understanding the origin and evolution of dengue viruses and helpful in predicting disease severity during possible future outbreaks.

Generally, patients with mild DF recover without hospitalization, and treatment is usually symptomatic and supportive. Nevertheless, a small number of cases, particularly those who have previously been infected with other serotypes of DENV, may develop a severe form of DHF or DSS which can be fatal if it is not properly managed. Patients suffering from a severe form of DHF or DSS may require blood transfusion. Blood products may be in short supply or not readily available at district hospitals. In the 2010 outbreaks, for example, almost all suspected dengue cases from other parts of the country were referred to STIDH, Kathmandu, due to the lack of the required blood products, particularly PRP. PRP should therefore be made easily accessible at district hospitals to meet the patients' need in areas where risk of dengue transmission is greatest.

Dengue infection is a relatively new disease in Nepal, hence much is not known about its frequency among the local population. To bridge this knowledge gap, health care providers must improve their clinical knowledge about dengue and DHF/DSS as well as be familiar with the geographical distribution of DENV in order to enhance their ability to adequately respond to a sudden and unexpected surge of patients due to DENV infection.

While safe, effective and affordable vaccine for DENV is anticipated, preventive measures that require an effective elimination of vectors and their breeding sites remain the only options to interrupt or control DENV transmission. The majority of the people are poorly educated; hence they know little about newly emerging diseases. Therefore, without involving local communities in the planning and implementation of vector control programs and health education, DENV transmission cannot be successfully controlled. Studies from Mexico, for example, have shown that educational campaigns and community-based vector control programs can significantly reduce the vector breeding places more effectively than the use of chemical spraying alone.[19,20] It is therefore wise to adopt these notable examples of success while designing vector control strategies for more effective dengue control.

CONCLUSIONS

Dengue virus infection has now increasingly becoming an emerging disease in Nepal. Current outbreaks of dengue fever in several districts underscore the need for urgent and comprehensive DENV surveillance in order to identify the current status of the disease burden and the high risk areas to be targeted for immediate implementation of preventive measures. Although DENV infection is a relatively new disease in Nepal, the time has come to recognize it as a major public health problem. Therefore, the state and stakeholders should come up with a campaign to promote public awareness so as to prevent or respond to possible outbreaks of DENV in the future.

Key points:

Dengue is an emerging disease in Nepal.

It is rapidly spreading into new areas across the country.

All four DENV serotypes are circulating in Nepal.

A subsequent DENV infection with a different serotype can lead to severe form of DHF/DDS.

No specific antiviral treatment is available.

Treatment is symptomatic and supportive.

A nationwide integrated epidemiological-entomological surveillance needs to be put high on the priority by health policy-makers.

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