Study of Clinical and Laboratory Profile in Patients with Dengue Fever at a Tertiary Care Center in Central Nepal

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ABSTRACT

Introduction: Dengue is a mosquito-borne viral disease transmitted from person to person by Aedes mosquitoes which result in a wide spectrum of disease severity ranging from influenza-like illness (dengue fever; DF) to the life-threatening dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS). Terai regions of Nepal were focal epidemics of Dengue infections during the outbreak in 2010, 2013, and 2016. Dengue infections have been reported in the valleys of upland Hill regions at an altitude of 2500 m above sea level in Nepal.

Methods: A cross-sectional study was carried out among febrile patients in Nepal Police Hospital (NPH), from 1st Baisakh 2076 to 30th Chaitra 2076. Blood samples were collected from dengue presumed cases and tested against dengue specific IgM antibody and/or NS1 antigen. Clinical examination findings were recorded, hematological and biochemical parameters tests were done among the patients who fulfilled the inclusion criteria.

Results: A total of 87 dengue cases were included in the study during the study period. Out of these, the majority were males (85.05%) from Kathmandu (38/87; 43.67%) seen in the month of Asoj (40/87; 45.98%). Fever was the major symptom (100%) followed by myalgia (52.87%), headache (45.97%), retro-orbital pain (12.64%), bleeding manifestations (9.19%). Common hematological abnormalities were thrombocytopenia and leucopenia in the critical phase. There was no case of dengue shock syndrome.

Conclusions: This study highlights the utilization of most common clinical and easily available laboratory profiles of dengue viral infections in particular season and place that could alert physicians to diagnose early to reduce morbidity and mortality due to dengue hemorrhagic fever and dengue shock syndrome.

INTRODUCTION

Dengue is a mosquito-borne viral disease. One modeling estimate indicates 390 million dengue virus infections per year (95% credible interval 284–528 million), of which 96 million (67–136 million) manifest clinically (with any severity of disease).1 Dengue is endemic in the WHO regions of Africa, the Americas,
the Eastern Mediterranean, South-East Asia, and the Western Pacific regions and the Caribbean. In the recent decades, the global incidence of dengue virus (DENV) infection has increased with increasing geographic expansion to new countries.

Seventy percent of the actual burden is shouldered by Asia. The significance of dengue hemorrhagic fever as a public health burden may be appreciated by Halstead’s Alexander D. Langmuir lecture in 1981: “Dengue hemorrhagic fever is an important cause of morbidity and mortality predominantly, but not exclusively, in children in tropical Asia. Over half a million persons have been hospitalized with this syndrome in the past 20 years, more than 200,000 in the past two years alone”. Nepal is a landlocked country situated in the central Himalayas area of South Asia. The dengue-wave spread from the Terai region and was detected every year in that particular Terai region. Chitwan and Rupandehi districts in the Terai region of Nepal were focal epidemics during the outbreak in 2010, 2013, and 2016. Not only in the lowland inner Terai region (Parsa district), which is 300 m below sea level, DENV have been reported in the valleys of upland Hill regions at an altitude of 2500 m above sea level.

Dengue infections caused by the four antigenically distinct dengue virus serotypes (DENV1, DENV2, DENV3, DENV4) of the family Flaviviridae are the most important arbovirus diseases in humans, in terms of geographical distribution, morbidity, and mortality. The infection is transmitted from person to person by Aedes mosquitoes. Dengue infections may be asymptomatic or may lead to an undifferentiated fever (or viral syndrome), Dengue Fever (DF), or Dengue Haemorrhagic Fever (DHF). Ae. Aegypti is the most efficient of the mosquito vectors because of its domestic habits. Other Aedes mosquitoes capable of transmitting dengue include Ae. albopictus, Ae. Polynesiensis and several species of the Ae. Scutellariscomplex. Among the two competent vectors of the disease, Aedes aegypti, and Aedes albopictus, the former is the primary vector for transmission among humans and is distributed only in the lowland Terai region of Nepal, whereas A. albopictus is found throughout Nepal.

According to the US Centers for Disease Control and Prevention (CDC) and the WHO dengue guidelines, the clinical features of DF and DHF are sudden onset of fever, severe headache, myalgia and arthralgia, leucopenia, thrombocytopenia, and hemorrhagic manifestations. It occasionally produces shock and hemorrhage, leading to death. Classic DF symptoms include fever, headache, retro-orbital pain, myalgia and arthralgia nausea, vomiting, and often a rash. Some DF patients develop the more serious form of the disease, DHF with symptoms that include a decline in fever and presentation of hemorrhagic manifestations, such as microscopic hematuria, bleeding gums, epistaxis, hematemesis, malena, and ecchymosis. DHF patients develop thrombocytopenia and hemoconcentration; the latter is due to an increase in the concentration of blood cells resulting from the leakage of plasma from the bloodstream. These patients may progress into Dengue Shock Syndrome (DSS), which can lead to profound shock and death if not treated. Advance clinical symptoms of DSS include severe abdominal pain, protracted vomiting, and a notable change in temperature from fever to hypothermia.

Infection with one serotype of DENV provides lifelong immunity to that serotype but results only in partial and transient protection against subsequent infection by the other three serotypes. It is well documented that sequential infection with different DENV serotypes increases the risk of developing DHF. Early clinical features of dengue infection are variable among patients, and initial symptoms are often non-specific; therefore, specific laboratory tests are necessary for an accurate diagnosis. The exact clinical and laboratory profile is crucial for diagnosis as well as the successful management of the patients. Aetiological diagnosis can be confirmed by serological testing and virus detection by isolation.
or molecular technique from the blood. Serological diagnosis by detection of anti-dengue IgM and IgG by enzyme-linked immunosorbent assay (ELISA) is now widely used to document primary and secondary infection. An ELISA assay for dengue NS1 antigen detection has been developed and commercial test kits are now available. Virus isolation, serotyping, or detection of dengue antigen by polymerase chain reaction (PCR) are very expensive and not widely available in our country. \(^6\) Physicians should be aware of the most common clinical as well as hematological and biochemical presentations which are important for the clinical management of patients and thus crucial for saving a life. Therefore, this study aimed to highlight the most common clinical features, hematological and biochemical findings of dengue cases. This study is an attempt to elucidate the clinical and laboratory profile of serologically confirmed cases of dengue fever in our hospital.

**MATERIALS AND METHODS**

**AREA OF STUDY**

Nepal Police Hospital, Panipokhari, Maharajgunj, Kathmandu, Nepal

**TYPES OF STUDY**

A Hospital-based cross-sectional prospective study from 1st Baisakh 2076 to 30th Chaitra 2076

**INCLUSION CRITERIA**

1. Febrile patients who were presumed for dengue infection based on 2009 WHO criteria.\(^{12}\)
2. Serologically confirmed with dengue specific IgM antibody and/or NS1 Antigen.

**EXCLUSION CRITERIA**

Cases confirmed as Malaria, Kala-azar, Typhoid fever, Leptospirosis were excluded from the study

A detailed history and careful clinical examination were performed on each patient. Laboratory investigations done were hemoglobin, total and differential leukocyte counts, platelet count, hematocrit, liver function tests, renal function tests. A Chest x-ray and ultrasonogram of the abdomen were done as required only. Blood parameters were monitored periodically as and when required till resolution. All patients were managed with regular monitoring of vitals, hematological, and biochemical parameters based on several standard guidelines. The study was approved by the hospital ethics committee and informed consent was obtained from each patient.

**STATISTICAL ANALYSIS**

Data were entered and analyzed using the SPSS 20.0 statistical software. A Descriptive statistic was used to calculate frequency and percentage. Data were presented using tables and figures.

**RESULTS**

During the study period, 87 patients diagnosed with dengue fever reported between 1st Baisakh 2076 and 30th Chaitra, 2076 were studied and analyzed. The majority of the patients were males (85.05%) (Figure 1). Study participant’s ages varied from 16 months to 71 years. The maximum number of patients was in the 20-29 age group (28/87; 32.19%) followed by the 30-39 age group (26.44%) as shown in table 1. The majority of the patients were from Kathmandu (38/87; 43.67%) (Figure 2). As shown in table 2, the maximum number of patients was seen in the month of Asoj (40/87; 45.98%) followed by the month of Kartik (22/87; 25.29%).

The commonest clinical feature was fever, which was seen in all patients (100%), followed by myalgia (52.87%), headache (45.97%), retro-orbital pain (12.64%), bleeding manifestations (9.19%), out of which, epistaxis was seen in 4 patients, rash (6.89%) and dry cough (5.74%) (Figure 3). Splenomegaly was seen in 5 patients (5.74%). Eight patients out of 87 (9.19%) were suffering from other preexisting diseases.
out of which 3 were hypertensive patients, 3 were diabetic patients and 2 had both hypertension and Type 2 Diabetes Mellitus.

As shown in table 3, The hematological profile of dengue patients was studied according to the febrile phase (1-3 days), critical phase (4-6), and recovery phase ≥7 days. The average mean total leucocyte count of all 87 patients on the febrile phase was 4387 cells/cumm, whereas 3374 cells/cumm and 5139 cells/cumm were recorded during the critical phase and recovery phase respectively. The minimum leucocyte count was 1700 cells/cumm, 1400 cells/cumm, and 3400 cells/cumm during febrile, critical, and recovery phases respectively. Similarly, the average mean platelet counts were 140800 cells/cumm 121600 cells/cumm, and 242353 cells/cumm during febrile, critical, and recovery phases respectively. Minimum Platelets counts during the febrile phase were 22000 cells/cumm and during the critical phase was 40000 cells/cumm.

As shown in table 4, leucopenia was seen in 31/87 (35.63%), 62/87 (71.26%), and 16/87 (18.39%) during febrile, critical, and recovery phase with significant leucopenia was seen during the critical phase (62/87; 71.26%). The majority of the patients with high hematocrit were seen in the critical phase (14/87; 16.09%). Similarly, thrombocytopenia was seen more during the critical phase (60/87; 68.96%) followed by the febrile phase (48/87; 55.17%) and the recovery (phase 22/87; 25.28%).

Biochemical parameters revealed that acute kidney injury was seen in 4 patients (4/87; 4.59%) with serum creatinine ranged from 1.3 mg/dL to 3.2 mg/dL which later on normalized during the recovery phase. Transaminitis were seen in 10 patients (10/87; 11.49%). The levels of ALT and AST ranged between 38-180 IU/L and 64-250 IU/L respectively.

All patients denied a history of previous dengue infections. Platelets rich plasma was transfused in 2 patients (2.29%) who presented with bleeding manifestations. One patient was admitted in ICU who had T2DM and Hypertension as co-morbid diseases. The Patient was discharged on request to another center where he died after 3 days of admission.

### DENGUE TABLE AND FIGURES

#### TABLE 1: Age-wise distribution of patients

| Age (years) | Number of dengue patients | Percentage (%) |
|-------------|---------------------------|-----------------|
| ≤9          | 1                         | 1.15            |
| 10-19       | 4                         | 4.59            |
| 20-29       | 28                        | 32.19           |
| 30-39       | 23                        | 26.44           |
| 40-49       | 15                        | 17.25           |
| 50-59       | 10                        | 11.49           |
| ≥60         | 6                         | 6.89            |

#### FIG 1: Gender wise distribution of dengue patients

#### TABLE 2: Month-wise distribution of patients

| Month   | Number of dengue patients | Percentage (%) |
|---------|---------------------------|-----------------|
| Bhadra  | 20                        | 22.98           |
| Asoj    | 40                        | 45.98           |
| Kartik  | 22                        | 25.29           |
| Mangsir | 5                         | 5.75            |

#### FIG 2: Area-wise distribution of patients
FIG 3: Clinical presentations of dengue patients

| Mean biochemical parameters | Febrile phase | Critical phase | Recovery phase |
|----------------------------|--------------|----------------|---------------|
| Total leucocyte count (TLC) | 4387 cells/cumm | 3374 cells/cumm | 5139 cells/cumm |
| Hemoglobin                 | 13.75 g/dl   | 14.39 g/dl     | 14.15 g/dl |
| Hematocrit                 | 39.73 %      | 41.27 %        | 41.38 %     |
| platelets                  | 140800 cells/cumm | 121600 cells/cumm | 242353 cells/cumm |
| ALT                        | 108.5 IU/L   | 132 IU/L       | 139.3 IU/L  |
| AST                        | 161.7 IU/L   | 177.4 IU/L     | 148.2 IU/L  |

TABLE 3: Mean changes in biochemical parameters in different phases of dengue infection

| Biochemical parameters | Febrile phase(n) | Critical phase(n) | Recovery phase(n) |
|------------------------|------------------|-------------------|------------------|
| Leucopenia (TLC < 4000/ cumm) | 31               | 62                | 16               |
| Hematocrit >45%        | 2                | 14                | 2                |
| Thrombocytopenia(< 150000/ cumm) | 48              | 60                | 22               |

Table 4: Changes in biochemical parameters in different phases of dengue infection

DISCUSSION

Nepal is a developing country. The progress in development is measured via proper planning and execution. But unplanned developments and execution can be hazardous to health too. The surge in many dengue cases over a few years is a consequence of unplanned urbanization and unchecked construction activities especially in cities like Kathmandu, Hetauda, and others. Poor sanitation facilities with fertile breeding areas for mosquitoes may be the reason for the increasing number of cases in Kathmandu in this study.

Dengue fever usually commences from mid-June and then there is a surge in September and ends in December. This study also had similar findings with the maximum number of patients were seen in the month of Asaj (40/87; 45.98%) followed by the month of Kartik (22/87; 25.29%), and few cases were seen till Mangsir. Annual seasonal variation trends of the dengue occurrence show, infections appear abruptly in July, just after the start of the rainy season, and cases peaks in August and September, which are considered to be the months with the most favorable climate for mosquitoes breeding. The knowledge of distinct seasonal trends of dengue prevalence/infections in Nepal helps in addressing precautions and public awareness programs during the specific months to control possible future outbreaks.

The majority of the patients (85.05%) in this study were males of age group 20-29 followed by 30-39. One can assume that compared to women who are generally confined within household works the male population is mostly involved in outdoor work activities for livelihood which makes them more likely exposed to Aedes spp. bites.

Fever was the most common presentation (100%), which is in accordance with other similar studies from India and South East Asia, followed by myalgia and headache which is in agreement with other studies too. Bleeding diathesis is a common
clinical presentation of dengue due to low platelet count and leakage from blood vessels. In this study mucosal bleeding was observed in most of the patients, which is in agreement with the other study. In another study, hemorrhagic manifestation in the form of petechiae only was reported. The variations in the clinical feature of several studies might be due to the difference in the serotype of the virus and its virulence factor causing infection.

Hematological profiles of the study were done according to the febrile, critical, and recovery phase of dengue infection. Leucopenia, thrombocytopenia, and raised hematocrit were seen more in the critical phase than other phases. Thrombocytopenia was the most common finding in the present study which is consistent with the other studies. Thrombocytopenia might be due to decreased production of platelets due to suppression of the bone marrow by a virus and also due to binding of dengue antigens to platelets and increased antibody-mediated immunological destruction of platelets. Leucopenia is one of the hematological parameters which occurs in people who were afflicted with dengue bone marrow suppression. Raised hematocrit was seen in the critical phase (14/87; 16.09%) in this study. Findings in this study are less than the observation of the other studies which reported a 50% and 27% 25 rise in hematocrit value. This may be related to increased severity from different serotypes of a virus with increased virulence than this study.

Acute kidney injury was seen in 4 patients out of 87 (4.59%), which resolved completely in the recovery phase, this is in accordance with other studies. Raised liver transaminases were seen in 10 patients (11.49%), out of which AST was increased more than ALT. Dengue virus is hepatotropic and also damages other organs: hence the observed pattern could be explained due to excess release of AST from damaged muscle cells (non-hepatic source) during infection that leads to more deranged AST than ALT. Infection with less virulent serotype may be the reason of less deranged transaminases in this study than others.

The overall mortality in this study was zero. However, one patient died in another center who was discharged from our center on the family’s request. Higher mortality rates shown in other studies could be due to re-infection and late presentation to the hospital.

CONCLUSION

Dengue infection is directly related to poor sanitation practices, unplanned urbanization, and insufficient public awareness programmes. In developing nations like ours where the majority of the population can’t afford expensive tests to detect and isolate virus particles and antigens, cheap laboratory tests that are easily available can help to identify severe infections promptly in particular season and place, as reflected by this study. Fever associated with myalgia, headache, retroorbital pain, erythematous rash, along with thrombocytopenia, leucopenia, elevated liver transaminases should prompt a clinician on the possibility of dengue infection. Early diagnosis, monitoring, and judicious fluid management hold a key in reducing the mortality due to dengue hemorrhagic fever and dengue shock syndrome.

LIMITATIONS OF THE STUDY

In this study, serotypes of the dengue virus were not identified. Hence the effects of infection with selective serotype couldn’t be determined. This study was done on patients who visited the hospital in Kathmandu only. This study didn’t cover all the dengue prone areas of the nation. As this study is a hospital-based cross-sectional study, subsequent follow up of the patients were not done for clinical and biochemical changes and effects of dengue reinfection over a period of time.

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