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**Original Research Article**

# An Outbreak of Dengue in Patna, Bihar: A study of 60 cases and review of literature

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## Abstract

**Background**: Dengue virus belongs to family *Flaviviridae*, having four serotypes that spread by the bite of infected Aedes mosquitoes.
**Materials and methods**: Dengue positive cases from June to December of two constitutive years, 2015-2016 were obtained, total number of cases were 60.
**Result:** Male and female were 36(60%) and 24(40%) respectively. They were negative for IgM and IgG. It denoted almost all cases were primary dengue infection. Out of total cases 28(46.6%) patients had initial presentation with thrombocytopenia, below 150,000/ul, minimum 20,000/. In first weak leucopenia with relative lymphocytosis, neutropenia, raised ALT and AST are important laboratory findings. From first weak onwards, petechial rashes due thrombocytopenia and erythematous skin patches due to increased vascular permeability are important features. The erythematous patches due to vasculopathy give a hot touch feeling. Rapid ELISA for NS1, IgM, and IgG could be false negative in 10% cases. For those dengue suspected cases ELISA, hemagglutination or PCR based investigations are warranted for diagnosis.
**Conclusion:** The study results are relevant in the characterization of biological markers in the evolution of the disease and can be used as markers for the most severe forms thereby enabling health professionals in taking early help with the adaption of therapeutic conduct for specific patients. It could be useful for making policy regarding control and prevention of dengue fever in state like Bihar where such type study is not till now published.
**Keywords:** Dengue, Aedes mosquitoes, NS1, DF/DHF, thrombocytopenia, vasculopathy.

## 1. Introduction

Dengue viruses (DV) belong to family *Flaviviridae* and there are four serotypes of the virus referred to as DV-1, DV-2, DV-3 and DV-4[1]. It is found mainly in areas of the tropic and sub-tropics. It is a positive-stranded encapsulated RNA virus and is composed of three structural protein genes, which encode the nucleocapsid or core (C) protein, a membrane-associated (M) protein, an enveloped (E) glycoprotein and seven non-structural (NS) proteins [2].

It is transmitted mainly by *Aedes aegypti* mosquito and also by Aedes *albopictus* [4]. All four serotypes can cause the full spectrum of disease from a subclinical infection to a mild self limiting disease, the dengue fever (DF) and a severe disease that may be fatal, the dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS). The WHO 2009 classification divides dengue fever into two groups: uncomplicated and severe (1), though the 1997 WHO classification is still widely used.

The 1997 classification divided dengue into undifferentiated fever, dengue fever (DF), and dengue haemorrhagic fever (DHF). Four main characteristic manifestations of dengue illness are *(i)* continuous high fever lasting 2-7 days; *(ii)* haemorrhagic tendency as shown by a positive tourniquet test, petechiae or epistaxis; *(iii)* thrombocytopoenia (platelet count $<100\times10^9$/l); and *(iv)* evidence of plasma leakage manifested by haemoconcentration (an increase in haematocrit 20% above average for age, sex and population), pleural effusion and ascites, *etc* [5,6].

Approximately 2.5 billion people live in dengue-risk regions with about 100 million new cases each year worldwide [1,7]. Dengue disease presents highly complex pathophysiological, economic and ecologic problems. In India, the first virologically proved epidemic of dengue fever (DF) occurred in Calcutta and Eastern Coast of India in 1963-1964[7,8]. All four serotypes cause dengue fever, a severe flu-like illness; usually without cold and cough. The disease is prevalent in third world tropical countries and now spreading to sub-tropical developed countries. WHO estimated that 50-60 million cases of dengue fever occurs worldwide each year, including serious clinical types: Dengue hemorrhagic fever and dengue shock syndrome [1]. Primary infection manifests as self-limiting mild to severe fever, lasting for 5-7 days, severe headache with pain behind eyes muscle, joint, rash and vomiting. Secondary infection is more common in Southeast Asia, Including India and South America. Primary dengue infection is detected with specific NS1 antigen in 0-9 days after the onset of symptoms; the symptoms usually persist for 15 days [9,10].

The early diagnosis of dengue reduces risk of complication of severe clinical types DHF and DSS, especially in endemic countries. IgM antibodies are not detected till 5-10 days in case of primary infection and till 4-5 days in secondary infection after onset of illness. In some cases IgM level could be undetectable or weakly detectable. IgG appears after 14 days and persists for life in primary infection and rise within 1-2 days after onset of symptoms in secondary infection [11,12].

Secondary infection is more serious and may lead to DHF and DSS. The major clinical symptoms include body ace, high fever, hemorrhagic events, and respiratory failure. Fatality rate can be as high as 40%[13-15]. Serologic cross reactivity with other flavivirus infection like Japanese encephalitis is common. Yellow fever has no occurrence In India.

But chikungunya clinically mimicking dengue fever has not serologic cross reactivity with dengue. More confirmatory diagnostic tests like PCR and hemagglutination inhibition test should be done in negative cases if clinically warranted. Infection confers lasting immunity to the serotype involved. Until recently, the most commonly used serological techniques for the routine diagnosis of dengue virus was the hemagglutination inhibition (HI) test and capture immunoglobulin M (IgM) by an enzyme-linked immunosorbent assay (ELISA). The HI test is the reference test recommended by the World Health Organization (WHO) to discriminate between primary and secondary dengue virus infection [1].

Secondary infections are characterized by the presence of HI antibodies in acute-phase samples and by high titers of HI antibodies (>1:1,280) in serum from convalescence phase serum samples. For each pair of serum samples, the first sample is collected during the acute phase (**days 1** to 5), second sample is collected during the convalescent phase, 7 days or more after the onset of fever[1,17-19].

According to the ADE hypothesis, secondary dengue virus infections are risk factors for DHF/dengue shock syndrome. There are thus two reasons to find a simple test to distinguish between primary and secondary infection with early serum samples. The first reason is to be able to carry out an epidemiological study to check whether the incidence of severe cases of dengue is significantly higher among secondary infections than among primary infections.

The second reason is to know the immunological status of patients to allow clinicians to take it into account in the progression of the disease until the ADE hypothesis has been confirmed or disproved. DV antibody reactivity patterns serve as useful tools for classifying patients as having primary or secondary DV infection. Detection of DV IgM in the absence of DV IgG (i.e., an IgM-positive/IgG-negative reactivity pattern) is a clear indicator of primary DV infection. Similarly, an $IgM^+IgG^+$ pattern combined with low IgG avidity accurately identifies primary DV infection .An $IgM^+IgG^+$ reactivity pattern with high IgG avidity is an accurate marker of secondary infection among patients whose serum samples are collected within a month of symptom onset[20-22].

**1.1 Pathogenesis**

Pathogenesis could be understood by cellular and tissue tropism. Cellular tropism: three types of cells are involved: (1) immune cells (2) endothelial cells (3) cells of liver and other organs [27-30]. In immune system, primarily monocytes/macrophages are infected, responsible for cytokine release syndrome [27]. The mechanisms that have been considered to cause DHF include antibody-dependent enhancement (ADE) T cell response and a shift from Type 1 T helper (Th-1 ) to type 2 T helper (Th-2) responses[31-35]. Th-1 cells produce interferon-gamma, interleukin (IL)-2, and tumour necrosis factor (TNF)-beta, which activate

macrophages and are responsible for cell-mediated immunity and phagocyte-dependent protective responses. type 2 Th (Th-2) cells produce IL-4, IL-5, IL-10, and IL-13, which are responsible for strong antibody production, eosinophil activation, and inhibition of several macrophage functions, thus providing phagocyte-independent protective responses[34,35]. The combined effect of all of these is cytokine release syndrome resulting in movement of body fluids in extravascular space. Various cytokines have been implicated in the immuno-pathogenesis of DF/DHF.

It has been suggested that in dengue a Th1 response is linked to recovery from infection while a Th2 type response leads to severe pathology and exacerbation of the disease. Vasculopathy is characterized by attachment of major nonstructural protein NS-1 to membrane of endothelial cells leading to cell retraction and increased vascular permeability, with clinical manifestation of hemorrhage and ultimately shock in few cases. The microvasculature of lung and gut is preferentially affected, that is radiologically manifested with pleural effusion and ascites.

In liver, hepatocytes and kupffer cells are affected, producing hypoxia and release of AST and ALT, however severe hepatic damage is not established till now. So coagulopathy is not due to factor deficiency. Secondary dengue infection with different serotype is more serious due to phenomenon of antibody enhancement of disease. The production of excessive antibody against NS1 antigen by memory cells is one of the probable cause of DHF/DSS .Therefore antibody is not protective. Also autoantibody effect is seen, due to cross-reactivity with other tissue of human being.

DV-2 inhibits *in vitro* megakaryopoiesis and induces apoptotic cell death in a subpopulation of early megakaryocytic progenitors which may contribute to thrombocytopenia in dengue disease. In another study it was shown that DV-2 may directly interact with and activate platelets and thus may be responsible for thrombocytopenia.

Still the exact cascade of mechanisms involved in dengue disease pathogenesis remains unexplained and lot more needs to be done.

## 2. Methods and Materials

Dengue infections were retrospectively studied in diagnostic centers of Government Medical colleges of Bihar. Dengue positive cases from June to December of two constitutive years, 2015-2016 were obtained, total number of cases were 60. Male and female were 36(60%) and 24(40%) respectively. Male female ratio was 1.5:1.out of 60 cases, 41 (68.4%) patients presented with varying degree of leucopenia and 2 patients had initial neutropenia.

Those patients presented within first week of fever and all except one were positive for NS1 rapid ELISA method. They were negative for IgM and IgG. Out of total cases 28(46.6%) patients had initial presentation with thrombocytopenia, below 150,000/ul, minimum 20,000/. The variables selected were: hemoglobin, hematocrit, leukocytes, lymphocytes, platelets, ALT and AST.

Peripheral blood smears done in all cases to get manual count of platelet and also to rule out other possible causes of thrombocytopenia. In two cases bone marrow aspiration were done.

## 3. Result

The results of 60 patients with clinical and laboratory diagnosis of dengue fever were analyzed; 36(60%) were male and were 24(40%) female (Table 1 and 2). The ages ranged from 6 to 56 years (Table 1 and 2). Male female ratio was 1.5:1.out of 60 cases, 41 (68.4%) patients presented with varying degree of leucopenia and 2 patients had initial neutropenia. Those patients presented within first week of fever and all except one were positive for NS1 rapid ELISA method. They were negative for IgM and IgG. Out of total cases 28(46.6%) patients had initial presentation with thrombocytopenia, below 150,000/ul, minimum 20,000/ul. In all cases manual platelet count was done. In two cases bone marrow aspiration smears showed normal megakaryopoiesis.

**Table 1: Hematological parameters in NS1 positive febrile dengue cases 2015**

| Case No. | Age /Sex | TLC | RBC | HB | HCT | PLT |
|---|---|---|---|---|---|---|
| **1** | 48Y/F | 3.2 | 5.82 | 16.5 | 46.2 | 120 |
| **2** | 28Y/M | 3.4 | 4.63 | 11.6 | 35.1 | 160 |
| **3** | 26Y/M | 5.5 | 5.43 | 15.2 | 46.1 | 65 |
| **4** | 6Y/M | 1.9 | 5.90 | 16.3 | 46.2 | 20 |
| **5** | 19Y/M | 2.8 | 5.08 | 15.1 | 44.8 | 120 |
| **6** | 22Y/M | 3.3 | 4.93 | 14.3 | 43.3 | 140 |
| **7** | 54Y/M | 5.9 | 5.20 | 15.9 | 46.8 | 155 |
| **8** | 45Y/M | 5.8 | 5.08 | 15.8 | 46.2 | 140 |
| **9** | 55Y/M | 3.6 | 3.97 | 12.2 | 36.8 | 65 |
| **10** | 18Y/M | 4.9 | 4.67 | 13.1 | 39.1 | 160 |
| **11** | 48Y/F | 2.8 | 5.08 | 15.8 | 47.2 | 68 |
| **12** | 62Y/F | 2.7 | 5.10 | 15.9 | 46.5 | 70 |
| **13** | 47Y/F | 2.4 | 5.28 | 11.2 | 34.8 | 190 |
| **14** | 25Y/F | 2.5 | 4.80 | 10.9 | 33.9 | 220 |
| **15** | 33Y/F | 3.8 | 5.09 | 14.3 | 46.2 | 85 |
| **16** | 32/M | 3.4 | 5.05 | 14.3 | 44.8 | 65 |
| **17** | 20Y/M | 3.4 | 5.08 | 14.3 | 44.8 | 100 |
| **18** | 25Y/M | 3.8 | 5.29 | 14.4 | 44.9 | 66 |
| **19** | 15Y/M | 3.9 | 5.28 | 14.3 | 45.8 | 95 |
| **20** | 8Y/M | 3.4 | 5.28 | 14.3 | 43.8 | 140 |
| **21** | 12Y/M | 2.7 | 5.35 | 15.4 | 47.5 | 250 |
| **22** | 31Y/ M | 2.6 | 5.34 | 11.7 | 35.6 | 290 |
| **23** | 30Y/M | 3.8 | 3.65 | 14.0 | 44.5 | 180 |
| **24** | 40/F | 3.4 | 3.65 | 13.5 | 40.5 | 160 |

**TLC: total leucocyte count RBC: Red blood cell count HB: hemoglobin HCT: hematocrit, PLT: platelet count**

**Table 2: Hematological parameters in NS1 positive febrile dengue cases 2016**

| Case No. | Age /Sex | TLC | RBC | HB | HCT | PLT |
|---|---|---|---|---|---|---|
| 1 | 45y/F | 3.3 | 6.56 | 17.1 | 51.5 | |
| 2 | 48Y/M | 2.8 | 3.84 | 11.1 | 33.1 | 100 |
| 3 | 47Y/M | 4.2 | 3.87 | 11.1 | 35.1 | 160 |
| 4 | 26Y/M | 3.3 | 6.56 | 17.1 | 51.5 | 90 |
| 5 | 19Y/M | 2.3 | 4.98 | 15.7 | 45.5 | 105 |
| 6 | 21Y/M | 3.9 | 5.26 | 16.3 | 49.9 | 160 |
| 7 | 32Y/F | 4.1 | 4.01 | 9.8 | 31.9 | 240 |
| 8 | 18Y/F | 2.9 | 3.84 | 11.1 | 33.1 | 100 |
| 9 | 50Y/M | 7.1 | 4.68 | 14.2 | 43.5 | 200 |
| 10 | 46Y/M | 6.1 | 4.35 | 12.9 | 41.1 | 160 |
| 11 | 24Y/F | 5.4 | 3.77 | 11.6 | 35.2 | 200 |
| 12 | 22Y/M | 3.1 | 4.7 | 15.9 | 46 | 155 |
| 13 | 25Y/M | 3.9 | 3.43 | 10.3 | 32.7 | 160 |
| 14 | 16Y/M | 3.3 | 4.43 | 11.8 | 36.3 | 160 |
| 15 | 28Y/M | 3.8 | 4.4 | 13.8 | 41.7 | 145 |
| 16 | 33Y/M | 3.9 | 5.10 | 16.1 | 49.1 | 160 |
| 17 | 44Y/M | 2.6 | 4.6 | 14.5 | 43.2 | 120 |
| 18 | 18Y/M | 3.1 | 3.94 | 11.6 | 35.1 | 110 |
| 19 | 25Y/M | 7.1 | 4.68 | 14.2 | 43.5 | 200 |
| 20 | 42Y/F | 2.7 | 4.12 | 11.5 | 35.3 | 80 |
| 21 | 10Y/M | 6.1 | 4.09 | 11.9 | 36.5 | 160 |
| 22 | 52Y/F | 2.6 | 3.16 | 10.1 | 31.8 | 180 |
| 23 | 40Y/M | 3.5 | 4.70 | 15.9 | 46 | 155 |
| 24 | 13Y/F | 7.8 | 4.16 | 12.6 | 37.4 | 160 |
| 25 | 30Y/M | 6.2 | 4.10 | 12.0 | 38.5 | 170 |
| 26 | 51Y/M | 2.8 | 4.43 | 11.8 | 36.3 | 160 |
| 27 | 34Y/F | 6.1 | 4.09 | 11.9 | 36.5 | 160 |
| 28 | 17Y/M | 4.8 | 4.70 | 14.4 | 43.6 | 200 |
| 29 | 48Y/M | 3.9 | 3.43 | 10.3 | 32.7 | 160 |
| 30 | 38Y/F | 7.5 | 3.76 | 10.2 | 32.1 | 230 |
| 31 | 26Y/F | 3.9 | 3.43 | 10.3 | 32.7 | 160 |
| 32 | 54Y/M | 6.9 | 3.76 | 10.2 | 32.1 | 230 |
| 33 | 49Y/F | 3.3 | 4.20 | 12.3 | 38.4 | 140 |
| 34 | 29Y/F | 3.6 | 3.76 | 10.2 | 32.1 | 230 |
| 35 | 50Y/F | 2.8 | 4.43 | 11.8 | 36.3 | 160 |
| 36 | 18Y/M | 6.5 | 4.16 | 12.6 | 37.4 | 160 |

**TLC: total leucocyte count RBC: Red blood cell count HB: hemoglobin HCT: hematocrit, PLT: platelet count**

## 4. Discussion

Dengue fever is an infectious disease which is difficult to distinguish clinically from other viral fever prevalent in our region. This study aimed at analyzing clinical and epidemiological data and laboratory dynamics in order to try to identify biomarkers that are predictive of severity.

In our study, early dengue fever cases with NS1 positive were prevalent possibly because the out patients were referred for evaluation of febrile cases presented with malaise, severe body ace or joint pain.

The frequency of dengue fever in the study was higher in the group aged 20 years old or over. There was a predominance of men in this study; in most published studies, there is no significant difference in the proportions by gender [37,38].

Regarding clinical forms of disease, due to mostly outpatients, early CBC findings did not show significant change on HB, HCT, platelet count, TLC and DLC. However inpatients were followed up with serial CBC and LFT showed progressive change in hematological parameters and liver enzymes with raised HB, HCT, decrease TLC count and raised SGPT, SGOT. These changes were more evident in second and third weeks, after that normalization started in uncomplicated cases.

In the clinical forms of dengue, only DHF and DSS showed peak elevations in Hb and HCT during the course of the disease, a change most likely attributed to hemoconcentration, which can lead to hypovolemic shock.[4]

It was found that CD began with normal TLC and normal differential count. Leucopenia was more pronounced in the CD and DHF clinical forms and in patients of 20 years old or older, similar to other published results[40,41].

In the hemorrhagic and severe forms, mild thrombocytopenia occurred from the onset of symptoms and progressive decline in count with progression of the disease. This was more evident in the older age group. In CD, thrombocytopenia started late. This result is in agreement with the literature, which reports moderate or severe thrombocytopenia in DHF[43,44]. The inflammatory responses to dengue are attributed to immune complex formation, complement activation and the release of cytokines into the circulation in a phase prior to the most serious forms of the disease, so called cytokine release syndrome. The cytokine release syndrome attributes features of joint pain, severe body ace and weakness, gastritis, hepatitis. The mechanisms underlying the bleeding in DHF are multiple including vasculopathy, thrombopathies and DIC. Thrombopathy consists of thrombocytopenia and platelet dysfunction.

One case of atypical Dengue occurred in chronic ITP without hemorrhage with initial platelet count <10,000/ul. He was put on steroid and he responded well and after two doses of dexamethasone 40 mg IV OD, his platelet raised >100000.00/ul. It denotes that course of ITP is not changed or deteriorated due to dengue infection. Same steroid response or better response could be expected. Perhaps knowing the autoimmune nature of dengue steroid could be useful in progressive thrombocytopenia. However present WHO recommendation is not advocating steroid use. This type good response was previously not seen but when he was dengue infected response of steroid was better. This could be milestone in treatment of dengue when platelet count is not raised spontaneously. However author had not used steroid in isolated dengue infection. Further

study is needed to establish use of steroid in isolated dengue cases

One case presented with lobar lung consolidation and platelet count 20, 000/ul/ul. Another atypical case presented with cutaneous rashes not due to thrombocytopenia but capillary and arteriolar –capillary leak of plasma and RBC. Yet another case presented with upper gastrointestinal bleeding due to thrombocytopenia and one SDP was given along with trenaxamic acid. In this case diagnosis was done by ELISA method, rapid ELISA was negative for dengue. This denotes limitation of rapid ELISA. In all cases, complication started with subsidence of fever i.e. after first week.

AST levels increased at the onset of symptoms in all clinical forms and remained at varying but high levels during disease evolution. ALT started with above normal values in the severe form and remained steady throughout the course of the disease; in the classic and hemorrhagic forms, the increase in liver enzymes occurred progressively [28].

Similar results were obtained by other authors, who showed that both AST and ALT exhibited higher than average values in under 15-year-old patients with DHF. Another author found a significant increase in transaminases, especially AST, in children with dengue when compared to a control group with other febrile (non-dengue) illnesses. In our experience of two cases bone marrow smears showed normal megakaryopoiesis. Although bone marrow study is not recommended in dengue infection, it could be useful in refractory cases of thrombocytopenia in dengue infection. Manual platelet count and PBS are necessarily done in all cases to know exact value of platelet and also rule out other associated hematological problems.

An increase in ALT (≥ 40 IU) in children with dengue fever can be considered a predictive marker for shock syndrome. The liver is one of the target organs for dengue and clinical manifestations of hepatic dysfunction can occur during the course of this disease. The liver is deprived of oxygen leading to lesions of the parenchyma, in which the injured hepatocytes release transaminases [28,40] In most cases, the high levels of transaminases show the degree of hepatocellular injury, prolonging the clinical course of the disease; however, there is no correlation with prognosis. It is an acute viral infection presetting as flu-like symptoms except cold and cough

## 5. Conclusion

Dengue fever evolves with laboratory alterations starting on day one with NS1 positivity, subsequent biochemical and hematological changes become evident on the 3rd day and becoming most evident on the 5th day with values restored to normal by the 11th day to 15th day. The disease was more severe in individuals aged 15 years and older with a more pronounced and persistently raised liver enzymes (AST, ALT) and hemoconcentration, manifested by high RBC count, hemoglobin and hematocrit. The study results are relevant in the characterization of biological markers in the evolution of the disease and can be used as markers for the most severe forms thereby enabling health professionals in taking early help with the adaption of therapeutic conduct for specific patients. It could be useful for making policy regarding control and prevention of dengue fever in state like Bihar where such type study is not till now published.

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