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Original Research Article

Haematological profile of dengue fever

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ABSTRACT

Background: Dengue is a viral illness that is increasingly becoming endemic in India. This study aimed to study the haematological profile of patients diagnosed with dengue infection in a tertiary care hospital.
Methods: 89 patients suspected of having dengue illness were followed. Out of which those confirmed by positive serology were followed and studied in detail (n=46).
Results: Common clinical symptoms were fever, vomiting, and abdominal pain. Common haematological abnormalities were thrombocytopenia and leucopoenia. All patients improved clinically with improvement of biochemical and hematological parameters. None of the patients died in this series.
Conclusions: Dengue Fever continues to be a significant health problem especially in Northern region of India. A sharp vigilance is required by concerned authorities to prevent and minimize any future outbreak. It is extremely important to implement and maintain an effective, sustainable and community based disease prevention program.

Keywords: Dengue, Fever, Leukopenia, Thrombocytopenia

INTRODUCTION

Dengue infection is one of the most common mosquito borne viral diseases of public health significance. It is caused by one of the four serotypes of the dengue virus (DEN-1, DEN-2, DEN-3 and DEN-4) also referred to as an arbovirus (arthropod-borne viruses) that belongs to the genus *Flavivirus* of the family Flaviviridae. The virus serotypes are closely related but antigenically distinct. It is a disease with a wide clinical spectrum and a wide variety of presentations, ranging from asymptomatic to an undifferentiated fever to the more severe life threatening forms such as Dengue hemorrhagic fever (DHF)/ dengue shock syndrome (DSS).

Transmission to humans occurs by the bite of the female *Aedes aegypti* mosquito infected by one of four serotypes of the virus. This mosquito, a domestic species adapted to urban conditions, is the main vector in India.

In recent decades, the incidence of dengue infection has increased around the world and has become a major international public health concern. The disease is now endemic in more than 100 tropical and sub-tropical countries. DF is endemic in India, especially in the northern regions.

Early clinical features of dengue infection are variable among patients, and initial symptoms are often non-specific resembling any viral illness. Therefore, specific laboratory tests are necessary for an accurate diagnosis. According to the US Centers for Disease Control and Prevention (CDC) and the WHO dengue guidelines, the classical clinical features include fever, headache, retro-orbital pain, myalgias and arthralgias, 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, melina, and ecchymosis. These patients may progress into 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.[1]

Clinical Diagnostic criteria of DHF (WHO)

- Sustained high fever lasting 2–7 days;
- Petechiae or epistaxis with a positive tourniquet test
- Thrombocytopenia (platelet count $\leq 100\times10^9$/L); and
- Evidence of plasma leakage -hemoconcentration (an increase in hematocrit ≥20% above average for age, sex and population), pleural effusion and ascites.[2]

Apart from the plethora of clinical findings there are a number of specific microbiological, serological and molecular tests (viral isolation tests and serology for antibody examination). These specific tests are relatively expensive in a resource poor country like India.

In dengue fever a series of biochemical and haematological derangements are also commonly reported. Among hematological variables, hematocrit and thrombocytopenia is used as diagnostic modality. Leukopenia is the most prominent haematological change, sometimes with counts of less than $2x10^9$/L. However, there are reports of mild leukocytosis at the onset of the disease, with neutrophilia. Lymphocytosis is a common finding, with the presence of atypical lymphocytes.

Of biochemical variables, the most frequent changes occur in liver function tests such as in serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), Gamma-glutamyl transpeptidase and alkaline phosphatase levels, and serum albumin concentrations.[3-5]

Hence, the diagnosis of dengue fever is carried out based on clinical, epidemiological and laboratory data. In this context, the present study aimed to assess the hematological dynamics of patients with dengue fever in order to increase the sensitivity of the screening by healthcare professionals.

METHODS

The study included all patients diagnosed with dengue. The case definition was based on compatible clinical history and examination based on WHO criteria, confirmed by positive serology for dengue using the ELISA IgM capture method. All patients admitted in emergency medicine ward and inpatient ward of Government Medical College and Hospital from July 2016 till December 2016 with a suspected diagnosis of DF and DHF were followed (n=89). All cases confirmed by a laboratory diagnosis of dengue fever were studied in detail to determine age, gender, ethnicity, clinical and laboratory profile (n = 46, 06 females and 40 males). The various confirmation modalities used were IgM antibody capture ELISA and four-fold rise in antibody titres being done in the microbiology department (n = 38), RT-PCR detection of viral genomic sequence or by using rapid detection kits (n = 8) available at private labs. The haematological parameters were serially assessed.

Other data collected included clinical time of infection (month); days of hospitalization; course of illness and mortality rate. All patients had complete septic screening including blood, urine and stool culture and the blood film was checked for malarial parasites in both thick and thin films. Blood and platelet transfusions conducted were also recorded.

RESULTS

Demographic features

Among these 46 patients with confirmed diagnosis, 40 were males while the rest were females giving a male to female ratio of 6.6:1. Their ages ranged from 14 years to 60 years with a mean age of 43.97 years.

Table 1: Age distribution of patients with dengue fever (n = 46).

Age groups (years)	Number of cases
0-10	0
11-20	4
21-30	18
31-40	11
41-50	8
> 50	5
Total	46

Seasonal distribution

The onset of dengue fever in this region coincides with the onset of the monsoon season peaking in July-August as the rain and water logging results in good breeding grounds for the larvae of the vector.

Table 2: Seasonal distribution of patients with dengue fever (n = 46).

Month	Number of cases
July 2016	17
August 2016	22
September 2016	4
October 2016	1
November 2016	1
December 2016	1

In this study also, majority of the patients were in the months of July-August (n=39), followed by September (n=4) and one each in the subsequent months until early December.

Clinical profile

Fever was the most common clinical presentation, occurring in all patients on presentation. There was no specific pattern of fever and was usually high grade. Other common clinical features were headache (65.21%), myalgia (60.86%), abdominal pain. A maculopapular and erythematous rash was seen in 3 (6.52%) patients.

Table 3: Clinical manifestations of patients with dengue fever (n = 46).

Symptoms and signs	Number of cases
Fever	46
Headache	33
Myalgias	26
Vomiting	5
Diarrhea	3
Rash	3
Gingival bleeding	0
Gastrointestinal bleeding	0
Positive tourniquet test	0
Jaundice	0
Drowsiness	4
Hepatosplenomegaly	0

Relatively less common clinical features were vomitting, diarrhea and retro-orbital pain. None of the patients with positive serology reported any bleeding/hemorrhagic manifestations including ecchymosis, melina, hematemesis, etc. There was no mortality reported.

Laboratory profile

Hematological profile

The most common hematological abnormalities were thrombocytopenia and leukopenia.

Table 4: Profile of abnormal laboratory investigations in patients with dengue fever (n=46).

Investigation	No. of cases
Hematocrit ≥20% of normal	1
Platelet count >100,000 mm^3	8
Platelet count 50000-100000 mm^3	8
Platelet count <50,000 mm^3	23
White Blood Cells count <4x10^3/ mm^3	19
Partial thromboplastin time (PTT) >2-fold versus controls	10

Platelet count below <1 lakh /cumm was seen in 40 (86.9%) patients, out of which <50,000/cumm was seen in 17 patients. However only 5 patients had values less than <20,000/cumm. Another interesting finding is that severe thrombocytopenia was majorly seen in 20-30 age group.

Leukocytosis was observed in most patients on admission in the first days of the disease, followed by leukopenia from the 4th day of the disease, which was again more pronounced in the under 30-year-old age group. Sixteen (34.78%) patients had total white cell count below 4000/ cumm. Lymphocytosis was observed in all forms during the course of the illness which persisted till the time of discharge. The differential lymphocyte count varied from 21-61%. However, the absolute lymphocyte count varied from 1848-1891/ul and mean was 1884/ul.

A raise hematocrit of more than 20% was seen in only 1 (2.17%) patient.

Partial Thromboplastin time (PTT) and prothrombin time was normal in all 23 patients for which it was available.

Biochemical profile

Liver enzymes, both Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) were mildly elevated in 10 of the 21 (47.61%) patients for which it was done. Only 3 patients (14.28%) had mild hyperbilirubinemia.

Microbiological profile

Septic screening with blood, urine, sputum and stool culture was negative in all patients. Similarly, thick and thin blood film for malarial parasite was reported as negative in each patient.

Course of illness

All patients were treated symptomatically with intravenous fluids and analgesics. Three patients with platelet count of <20,000/cumm required platelet transfusion. The duration of stay in the hospital varied from 4 to 15 days with average of 7.3 days. All patients improved symptomatically and had significant improvement of biochemical and hematological parameters. There was no mortality seen.

DISCUSSION

A dengue is a hemorrhagic viral fever with serious consequences and can even be fatal. Hence, this study aimed at analyzing clinical and laboratory dynamics in order to increase the sensitivity of early diagnosis.

The frequency of dengue fever in the study was higher in the group aged 21-30 years old followed by 31-40 years. These results are similar to those of a epidemiological study.[3] This is most probably because of occupational exposure. There were very few children and no infant

was affected in our series. This is contrary to most other reported studies from India.[6,7]

There was a significant predominance of men in this study; which is similar to previous studies.[6] In most published studies, there is no significant difference in the proportions by gender.[8]

In our series, eighty patients were admitted with suspected diagnosis of dengue fever. Among these, 46 patients (57.5%) were confirmed to have the disease by ELISA and serology. It is possible that some of the other cases might have been missed.

Fever, headache and myalgia are the most frequent symptoms, as has been observed in other studies. Rash, hemorrhagic manifestations and positive tourniquet test were not reported in our study. None of the patients fulfilled WHO criteria for DHF.

It was found that early disease symptoms began with leukocytosis and leukopenia appearing later, in most of the patients by 3rd or 4th day of onset of fever. This result is in agreement with the literature.[9,10] Both Leukopenia and lymphocytosis and thrombocytopenia was more pronounced in the younger age group <30 years as compared to >30.

The pathogenesis of dengue fever is multifactorial. It includes direct effect of the virus on the endothelial cells leading to its activation. Also, there is abnormal immune response involving production of cytokines (cytokine storm), activation of T-lymphocytes and Antibody dependent enhancement. So, the possible hypothesis for more severe disease in young and well-nourished has been attributed to presence of robust immune mechanism which goes into overdrive.[11]

The various pro-inflammatory cytokines and inflammatory mediators are IL-8, C3a, C5a which are responsible for capillary and plasma leak i.e. hemoconcentration. IL 6 and 1 are responsible for coagulation and fibrinolysis leading to activation of coagulation cascade.

Literature states that there are two types of antibody involved. First is Neutralizing antibody which can inhibit viral replication, activate T-cells and complement system for viral destruction, often found in primary infection. The other is Enhancing antibody which helps viruses entering and replicating in target cells.[12]

The most significant laboratory abnormality seen in our patients was thrombocytopenia, as observed in other studies. The mechanism for thrombocytopenia and platelet destruction is again multifactorial. There is reduced platelet production because of direct damage to the megakaryocytic precursors (CFU-Meg). Also, there is increased peripheral destruction by pre-existing antibodies leading to immune complex formation with viral antigen and fixation on platelet surface leading to innocent bystander immune destruction. Antiplatelet antibodies (APA) are also produced by NS1 antigen which cross reacts with integrins and adhesins leading to platelet aggregation. Complement mediated lysis also plays an important role.

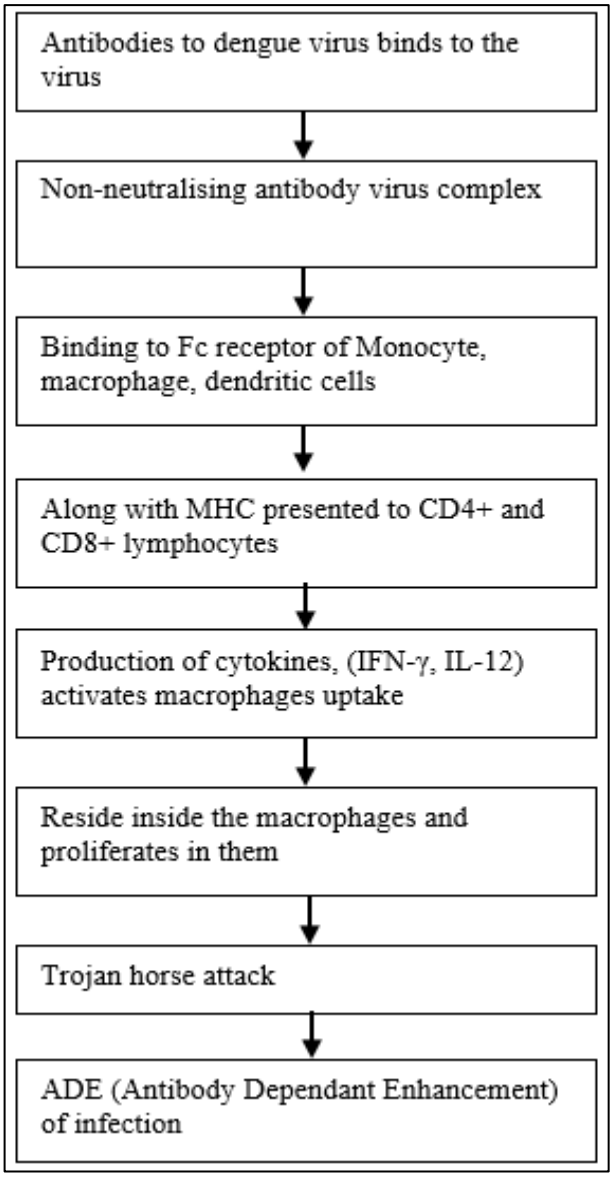

Figure 1: Antibody dependent enhancement.

Coagulopathy is also frequent in most patients with dengue fever. In present study however, there was incomplete data available and hence could not be verified. Disseminated Intravascular Coagulation (DIC) which is common in DHF was also not reported unlike other studies.[13,14]

The other important laboratory abnormality was raised liver enzymes seen in about 47.61% of our patients. Some patients could have been missed as LFTs are not available as an emergency biochemistry technique. Direct damage of liver by NS1 antigen leads to mid zonal

necrosis of hepatocytes responsible for elevated serum transaminases.[15]

3 patients received platelet and fresh frozen plasma transfusions. These patients recovered completely, although fatalities have been reported elsewhere in this region. An interesting observation in present study is that co-infection with malaria and dengue was not seen.

CONCLUSION

Both primary and secondary infection by any of the four DENV serotypes can cause DF; however, virus virulence is not the only factor to explain differences in host susceptibility to the disease and disease severity. Host immune response variations have been associated with polymorphism in the human genome, which may help explain why some patients develop end-stage complications in dengue disease and others only experience a mild form of the disease.

Hence dengue is a dangerous viral infection with complex immune mechanisms. Any disease prevention and control program should include education of medical community and the general population to reduce the impact of the epidemics.

Dengue fever does not have specific medical therapy hence clinical recovery monitoring is largely dependent on haematological parameters. This study concludes that parameter like platelet count, haematocrit, leukocyte count and coagulation studies aid greatly in clinical monitoring of patient. The study results are relevant in the characterization of evolution of the disease as well as the haematological dynamics involved and can be used as screening tools by physicians to chart early therapeutic response.

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