

Clinical and Hematological Effects of Dengue Viruses Infection

Badawy A. Abdul Aziz^{1,*}, Sharaf Elsayed Ali Hassanien¹, Adel Mahmoud Abdou²

¹Department of Hepatology, Gastroenterology and Infectious Diseases, Faculty of Medicine, Benha University, Egypt

²Department of clinical pathology Faculty of Medicine, Al Azhar University, Egypt

*Corresponding author: Badawyabdelkhalek123@gmail.com

Abstract Background: Dengue viruses infection is increasingly recognized as one of the world's emerging infectious diseases. Dengue usually presents with subclinical or mild infection to full blown dengue fever to dengue hemorrhagic fever and dengue shock syndrome. **Aim:** To evaluate clinical features, disease severity, laboratory findings in serologically confirmed cases of dengue fever in Muhammad Saleh Basharahil Hospital, Madina Road, Omra Gadida, Makkah, Saudi Arabia. **Methods:** This study was conducted on 83 patients with clinically suspected dengue fever. Hematocrit, platelet counts and total leucocyte counts were done serially in all the cases until they normalized. Liver function tests, chest X-ray, ultrasound abdomen, RFT, CT scan. The serological assay for dengue were performed using standard kits, dengue IgG/IgM Rapid Test is a solid phase immunochromatographic assay for the rapid, qualitative and differential detection of IgG and IgM antibodies to dengue virus in human serum or plasma. Patients with positive result for IgM or IgG antibodies against dengue virus were considered suspected dengue-positive group and the samples were confirmed by RT-PCR in a higher center. **Results:** Among 83 patients, 32 were confirmed dengue cases and the remaining 51 were considered as dengue negative and appropriate control. Among the positive dengue cases, 62.5(20/32) were male and 37.5(12/32) were female. Fever was present in all cases (100%) followed by myalgia in 93.75%. Macular, pruritic rashes was present in 28.125%. Abdominal pain was present in 25% of cases. Hemorrhagic manifestation in the form of petichae only was seen in 15.63%. Hepatomegaly was present in 12.5% and splenomegaly was present in 9.38. There was a significant difference in the total leucocyte count and platelets count, Significant differences were also seen in the liver function test and there was clear change in hematocrit value between dengue positive and dengue negative patients. **Conclusion:** Fever, myalgia and headache were the most common symptoms and hepatomegaly was the most common finding in the cases. Leucopenia, thrombocytopenia and hematocrit changes were significant features of dengue fever.

Keywords: dengue fever (DF), dengue hemorrhagic fever (DHF) thrombocytopenia

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1. Introduction

Dengue virus infection is increasingly recognized as one of the world's emerging infectious diseases [1,2]. Dengue is caused by the infection of dengue viruses, a flavivirus in the family of Flaviviridae. There are 4 serotypes of the virus [1,2]. *Aedes* mosquito serving as a vector for the transmission of the viruses. *Aedes aegypti* is the most important vector. *A. aegypti* is found in urban areas while *Aedes albopictus* predominates in the rural setting [3].

Case definition criteria for dengue fever were fever with rash, retro orbital headache, conjunctival congestion and myalgia. The criteria for dengue hemorrhagic fever (DHF) included a triad of hemorrhagic manifestations, platelet count of $< 1,00,000/\text{cmm}$ and clinical signs of plasma leakage observed in the form of pleural effusion, ascites or hypoproteinemia. The case definition criteria for dengue shock syndrome (DSS) included features of shock

in the form of rapid weak pulse and profound hypotension with systolic pressure of less than 90 mm Hg [4].

Laboratory diagnosis methods for confirming dengue virus infection may involve detection of the virus, viral nucleic acid, antigens or antibodies, or a combination of these techniques. After the onset of illness, the virus can be detected in serum, plasma, circulating blood cells and other tissues for 4–5 days. During the early stages of the disease, virus isolation, nucleic acid or antigen detection can be used to diagnose the infection. At the end of the acute phase of infection, serology is the method of choice for diagnosis [5].

Antibody response to infection differs according to the immune status of the host [5]. When dengue infection occurs in persons who have not previously been infected with a flavivirus or immunized with a flavivirus vaccine, the patients develop a primary antibody response characterized by a slow increase of specific antibodies. IgM antibodies are the first immunoglobulin isotype to appear. These antibodies are detectable in 50% of patients by days 3-5 after onset of illness, increasing to 80% by

day 5 and 99% by day 10. IgM levels peak about two weeks after the onset of symptoms and then decline generally to undetectable levels over 2–3 months. Anti-dengue serum IgG is generally detectable at low titers at the end of the first week of illness, increasing slowly thereafter, with serum IgG still detectable after several months, and probably even for life [6,7]. During a secondary dengue infection (a dengue infection in a host that has previously been infected by a dengue virus, or sometimes after non-dengue flavivirus vaccination or infection), antibody titers rise rapidly and react broadly against many flaviviruses. The dominant immunoglobulin isotype is IgG which is detectable at high levels, even in the acute phase, and persists for periods lasting from 10 months to life. Early convalescent stage IgM levels are significantly lower in secondary infections than in primary ones and may be undetectable in some cases, depending on the test used [8]. To distinguish primary and secondary dengue infections, IgM/IgG antibody ratios are now more commonly used than the haemagglutination-inhibition test (HI) [9].

A viral nonstructural protein, NS1, is released by infected cells into circulation and can be detected using monoclonal or polyclonal antibodies. The detection of NS1 is the basis of commercial tests, including rapid tests. These tests of reliable point of care diagnosis of acute dengue infection [10].

Dengue fever is known to affect hematological parameters and accordingly a simple clinical and hematological monitoring of the afflicted patients helps to reduce the morbidity and mortality. To validate this hypothesis, the present study was taken up in people attending a tertiary care centre at Makkah, Saudi Arabia.

2. Materials and Methods

2.1. Study Subjects

This study was conducted on 83 patients with clinically suspected dengue fever at the department of medicine in Muhammad Saleh Basharahil Hospital, Madina Road, Omra Gadida, Makkah, Saudi Arabia, from August 2015 to June 2016. The age group of patients was in the range of 13 - 68 years.

Hematocrit, platelet counts and total leucocyte counts were done serially in all the cases until they normalized. Liver function tests, chest X-ray, ultrasound abdomen, RFT, CT scan, ABG analysis were done according to clinical condition in selected cases. All cases were monitored and managed with IV fluids; blood products according to standard WHO guidelines [11].

2.2. Data Collection

Information regarding the suspected clinical pictures of dengue fever was recorded using a standardized questionnaire.

2.3. Diagnosis of Dengue Fever

The serological assay for dengue were performed using standard kits, dengue IgG/IgM Rapid Test is a solid phase immunochromatographic assay for the rapid, qualitative and differential detection of IgG and IgM antibodies to

dengue virus in human serum or plasma. This test provides only a preliminary test result. This test simultaneously detects and differentiate IgG and IgM antibodies to dengue virus (Den 1,2,3 and 4) in human serum and plasma by using a mixture of recombinant dengue envelop protein. Both the mouse monoclonal anti human IgG & IgM on the membrane and the dengue virus envelop protein gold will react specifically with IgG & IgM antibody to dengue virus for human serum or plasma. Patients with positive result for IgM or IgG antibodies against dengue virus were considered suspected dengue-positive group and the samples were sent for confirmation by RT-PCR in a higher center, while those that were not positive for the two assays were considered dengue negative.

3. Specimen Collection and Storage

Serum: collect the whole blood into the collection tube (Not containing anticoagulants) by venipuncture, leave to settle for 30 minutes for blood coagulation and then centrifuge blood at 3000 rpm for 10 minutes to get serum specimen of supernatant. With a 5 ul capillary pipette, add 5 ul of serum specimen drawn to black line into the square sample well, and then add 4 drops (90-120ul) of assay diluent to the assay diluent well, and then interpret test result in 15-20 minutes. Manufactured by SD; STANDARD DIAGNOSIS, INC. 156-68 Hagal-dong, Giheung-gu, Yongin-si, Kyonggi-do, Korea.

3.1. Ethical Considerations

Ethical clearance was obtained from the Muhammad Saleh Basharahil Hospital's ethics committee.

3.2. Data Analysis

Results are presented as mean \pm SD (standard deviation). Statistical analysis was carried out using SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc., Chicago, IL, USA) and chi-square and Student ttests were used to compare data.

P value >0.05 is non significant (NS)

P <0.05 is significant (S)

P ≤ 0.001 is highly significant (HS)

4. Results

A total of 83 adult cases who presented with fever and dengue-like illness were included in the study. Of these, 32 were confirmed dengue cases and the remaining 51 were considered as dengue negative and appropriate control. Among the positive dengue cases, 62.5% (20/32) were male and 37.5% (12/32) were female (Table 1 and Figure 1). The patients were presented most commonly by fever, rashes, headache, myalgia, abdominal pain, vomiting, loose motion, cough. The clinical and hematological features observed are in Table 1 - Table 4 and Figure 1, Figure 2. Fever was present in all cases (100%) followed by myalgia in 93.75%. macular, pruritic rashes was present in 28.125%. Abdominal pain was present in 25% of cases. Hemorrhagic manifestation in the form of petichae only was seen in 15.63%, other

significant bleeding manifestations (as hematemesis, melena, epistaxis and hematuria) were not present. Hepatomegaly was present in 12.5% and splenomegaly

was present in 9.38. Manifestations of increased capillary permeability in the form of ascites, pleural effusion and edema were not present.

Table 1. demographic and clinical data of dengue positive and negative cases

demographic & clinical presentation of patients	Dengue positive N=32	Dengue negative N=51
male	62.5%(20/32)	68.2%(35/51)
Female	37.5%(12/32)	31.37%(16/51)
Age(in years)	33.8±9.8	29.7±9.3
Fever	100%	100%
Rashes	28.125%(11/32)	7.84%(4/51)
Headache	40.63%(13/32)	21.57%(11/51)
Myalgia	93.75%(30/32)	43.14%(22/51)
Abdominal pain	25%(8/32)	13.72%(7/51)
Vomiting	40.63%(13/32)	43.14%(22/51)
loose motion	28.13%(9/32)	41.18(21/51)
cough	15.63%(5/32)	21.57%(11/51)
Bleeding manifestations (petichae only)	15.63%(5/32)	3.92%(2/51)
Heapatomegaly	12.5%(4/32)	5.88(3/51)
splenomegaly	9.38%(3/32)	15.67%(8/51)

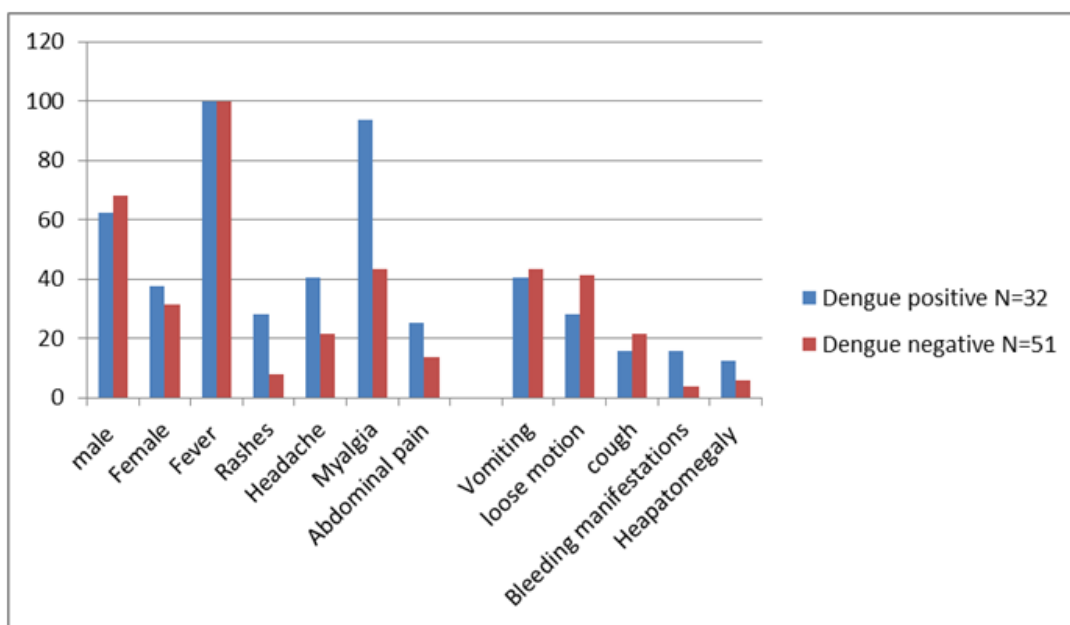


Figure 1. demographic and clinical data of dengue positive and negative cases

Table 2. Hematological parameters in dengue positive and negative cases

	Dengue positive N=32	Dengue negative N=51	P value
TC	4761.6±2739.2 (1600-13100)	7329±4864.3 (2400-13500)	<0.001(HS)
HB	13.56±1.49 (8.9-16.8)	12.91±1.39 (9.-15.8)	>0.05(NS)
Platelets	90148.2±41231.42 (15000-310000)	240264.1±78241.23 (62000-420000)	<0.001(HS)

Table 3. Haematocrit profile

HCT	Dengue positive N=32		Dengue negative N=51	
	%	NO	%	NO
>40	18.75	6	5.88	3
30-40	59.375	19	58.82	30
<30	21.88	7	35.29	18

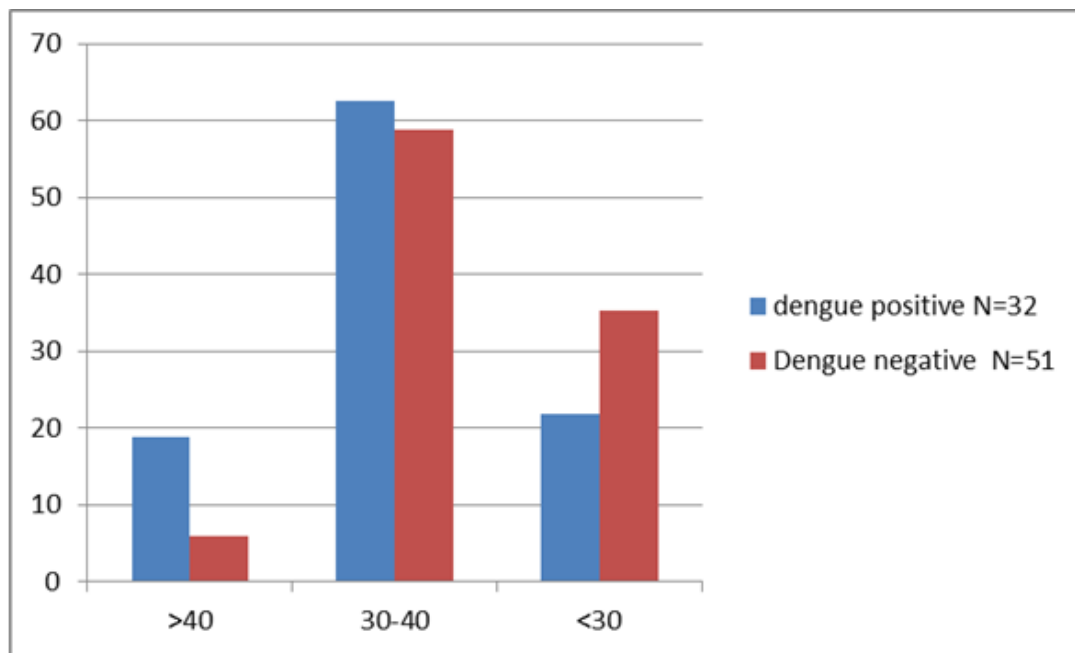


Figure 2. Haematocrit profile

Table 4. Biochemical parameters of liver and kidney function in dengue positive and negative cases

	Dengue positive N=32	Dengue negative N=51	P value
T.bilirubin	0.86±0.90 (0.19-4.1)	0.71±0.3 (0.21-3.1)	0.48(NS)
SGOT	141.2±136.9 (12-753)	27.26±12.35 (14-73)	0.0001(HS)
SGPT	79.87±89.38 (11-3894)	6.23±18.30 (9-125)	0.0001(HS)
urea	19.18±6.95 (2-39)	18.98±7.99 (7-37)	0.67(NS)
Creatinine	0.65±0.30 (0.41-1.55)	0.69±0.29 (0.4-1.39)	0.80(NS)

With respect to the hematological parameters, a significant difference in the total leucocyte count and platelets count was observed (in Table 2). Significant differences were also seen in the liver function test and expressed in Table 4. There was clear change in haematocrit values between dengue positive and dengue negative patients seen in Table 3.

5. Discussion

Dengue fever (DF) is a viral illness transmitted through the bite of an infected mosquito, usually *Aedes aegypti* or *Aedes albopictus* [5]. Dengue illness can range from a non-specific febrile illness, as in DF, to a more severe illness with bleeding tendency, thrombocytopenia, and plasma leakage [dengue haemorrhagic fever (DHF) [12,13].

In the present study the most common symptoms are fever, myalgia, headache, vomiting, rash and abdominal pain and this was in agreement with Banerjee et al., 2008 who reported in his study that The most common clinical features of dengue were fever and rash seen in 85% of patients [11]. Also Pervin et al., 2004 [14], reported occurrence of rash in 33 % of patients and myalgia reported in 84.5% of patients. Prathyusha et al., 2013 in his study, the common symptoms were fever 100%, abdominal pain (57.5%),vomiting(42.5%), significant bleeding(36.25%) myalgia(32.5%) and rash(28.75%) [16]. A study by Dhooria et al., 2008, the common symptoms described were fever 91%, vomiting 41%, abdominal pain

16%, poor intake 21%, significant bleeding 15% [17]. Also in study by Rategeri et al., 2005, the common symptoms were fever 100%, vomiting 82%, abdominal pain 61%, headache 22% [18]. According to Rahman et al., 2002, the common symptoms were headache 91%, myalgia 85% and vomiting 45%. In the present study hepatomegaly was present in 12.5 % [19]. And this was similar to Banjeree et al., 2008 who found in his study hepatomegaly was 15% [14]. Also in the present study splenomegaly was present in 9.38%, in a similar study by Prathyusha et al., 2013 splenomegaly was 5% [16]. Also Singh et al., 2005 found that hepatomegaly and splenomegaly were found in 10% and 5% of the cases [20]. In the present study the bleeding manifestation was in the form of petichae in 15.63%, In a study By Rategeri et al., 2005, GI bleeds were seen in 22%, patechiae in 18% [18].

In the present study haematocrit >40% was seen in 18.75%, 30 40% in 59.375 % and <30% in 21.88 %. In study by Parathyusha et al., 2013 haematocrit >40% was seen in 41.25%, 30 40% in 53.75 % and <30% in 5 % [16]. In a study by Anju et al., 1998 haematocrit >40% is seen in 18 %, >30 40% in 66 % and <30% in 16 % [21].

In the current study there was a good significant difference as regard total leucocyte (TLC) count between dengue positive and dengue negative patients (p value <0.001), It was observed that the dengue patients had a mean total leucocyte count of 4761.6±2,739 as compared to 7329±4,864 of dengue negative cases. And this was similar to a study by Jakribettu et al., 2015 who observed

that the dengue patients had a mean total leucocyte count of $4,984 \pm 3,082$ as compared to $7,926 \pm 2,760$ of dengue negative cases [22]. Also Prathyusha et al., 2013 observed Leucopenia (TLC < 4000/cu.mm) was in 53 (66%) cases with a mean leukocyte count of 2376 ± 1349 [13].

In the present study the platelets counts were significantly low in dengue positive cases compared to dengue negative cases ($p < 0.001$) as shown in Table 2, and this similar to many previous studies. Banerjee et al., 2008 observed that thrombocytopenia (platelets < 1,00,000/cmm) was seen in 19% of patients and the platelet count in those patients ranged between 44,000 – 1, 00,000/cmm [14]. Also thrombocytopenia was observed in dengue by studies by Jain, 2016, Arunagirinathan et al., 2015, Ratageri et al., 2005 and Sharma et al., 2014 [18,23,24,25]. Also thrombocytopenia observed by Prathyusha et al., 2013 that the mean platelets count was 55810 ± 43097 . [16].

In the current study the liver enzymes were significantly altered in dengue positive cases compared to negative cases ($p < 0.0001$) and this was similar to other studies by Sharma et al., 2014, Sahana et al., 2012 and Jagadishkumar et al., 2012 who observed that there were altered in liver functions in dengue. [25,26,27]. Also study by Jain, 2016 observed that elevated liver enzymes were observed in 38% of the patients and all patients with severe dengue had high values of enzymes [23]. Also there are many studies observed hepatic dysfunction in dengue (Prathyusha et al., 2013, Dhooria et al., 2008 and Faridi et al., 2010 [16,17,28].

6. Conclusion

Dengue fever is a self-limiting arboviral infection transmitted by vectors *Aedes aegypti* and *Aedes albopictus*. Fever, myalgia and headache were the most common symptoms and hepatomegaly was the most common finding in the cases. Hematological findings including TLC, platelets and hematocrit changes were observed in dengue positive cases.

Consent

All authors declare that written informed consent was obtained from the patient for publication of this paper.

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