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Clinical Study of Thrombocytopenia in Dengue Fever

Dr. Shankarappa R S
Associate Professor, Department of General Medicine, Sree Siddartha Medical College, Tumakuru, Karnataka

ABSTRACT

INTORODUCTION: Dengue is a mosquito-borne viral disease by Flaviviridae family causing wide spectrum of disease ranging from subclinical disease, severe flu-like symptoms to severe dengue associated with severe bleeding, organ impairment and/or plasma leakage with higher risk of death when not managed appropriately. WHO classifies as DF/ DHF/DSS earlier, at present as Dengue (with or without warning signs) and Severe Dengue. The virus may be detected by NS1antigen and by ELISA IgM IgG antibodies. Thrombocytopenia is one of the laboratory parameter in grading severity, a study is planned during an epidemic in south Karnataka region which would have a substantial impact on management by reducing morbidity and mortality associated with dengue.

AIMS AND OBJECTIVES: To correlate warning signs, laboratory parameters in different age groups, sex, with severity of thrombocytopenia with management.

MATERIAL AND METHODS: Prospective observational study conducted at south Karnataka for patients more than 15 years with Dengue NS1Antigen positive or IgM/IgG positive and Platelet count less than 1, 50,000 per dl. Detailed clinical history and detailed physical examination was recorded in a prescribed preform and subjected to Dengue NS1Antigen, IgM and IgG antibodies, Complete blood count, Random Blood Sugar, Urine analysis, Liver Function tests, Renal Function tests, Abdominal sonography, ECG and managed conservatively. Data was entered in Microsoft Office Excel Sheet 2010 and analyzed.

RESULTS: There are 124 thrombocytopenia, out of which 76 severe,34 moderate and 14 mild thrombocytopenia ,74(60%) are NS1 positive and 57(46%) are IgM positive,79 males (64%) and 45 females (36%), 49%are in 15-30 age (12% in 15-20, 37% in 21-30)and 20% in 31-40age, commonest clinical presentations along with fever are Headache 70%, myalgia 68%, nausea and vomiting 41%, arthralgia 27%, warning signs are abdominal pain 18%, bleeding manifestations 6%, restlessness 8%, altered sensorium 4%, bradycardia 26%, hypotension 17%, hepatomegaly 11%, abnormal laboratory parameters are leucopenia in 43%, abnormal renal function tests in 20%, elevated liver enzymes in 35% cases88%.There are 88% Dengue with warning signs,24% Severe Dengue with 17% circulatory collapse, 14% renal, 8% hepatic and 4% nervous involvement. Platelet transfusion done only in 27%.

CONCLUSION: Moderate to severe thrombocytopenia in young adults with NS1 / IgM positive is the commonest warning sign followed by abdominal pain, bleeding manifestations, restlessness, altered sensorium, leucopenia, bradycardia, hypotension, polyserositis, abdominal tenderness, hepatomegaly, elevated liver enzymes, hyperbilirubinemia, abnormal renal function tests . Majority require supportive management and maynot require platelet transfusion. Early recognition of warning signs and meticulous management can reduce the morbidity and mortality of dengue.

KEY WORDS: Severe Thrombocytopenia, Dengue NS1Antigen,Severe Dengue, warning signs

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INTORODUCTION

Thrombocytopenia is the commonest platelet abnormality encountered in clinical practice with variable clinical manifestations. Thrombocytopenia refers to reduction in platelet count below 1.5 lakhs per microliter in peripheral blood. The lifespan of platelet is around 7-10 days and about 10 percent are destroyed each day[1].Thrombocytopeniaresult from impaired platelet production, accelerated destruction, dilutional or splenic sequestration[2]. Clinicians may encounter many cases of thrombocytopenia with widespread use of automated cell counters and because platelet counts are prone to errors a single platelet count that is lower than normal should be confirmed by a second count and by inspecting the peripheral blood smear. Thrombocytopenia is classified based on platelet count as mild when platelet count is 1.0 to 1.5 lakhs/microliter, moderate when platelet count is 0.5 to 1.0 lakh/microliter and severe when platelet count is less than 0.5 lakh/microliter of blood. Dengue is a mosquito-borne viral disease caused by a virus of the Flaviviridae family (DENV-1, DENV-2, DENV-3 and DENV-4), transmitted by female mosquitoes mainly *Aedes aegypti* to a lesser extent, *Ae. Albopictus* which are also vectors of chikungunya, yellow fever and Zika viruses. Dengue causes a wide spectrum of disease ranging from subclinical disease, severe flu-like symptoms to severe dengue associated with severe bleeding, organ impairment and/or plasma leakage with higher risk of death when not managed appropriately.

WHO earlier classifies Dengue as DF/ DHF/DSS[3]. Dengue Fever (DF) is a patient having fever with two or more of be following: Headache, Retro-orbital pain, Myalgia, Arthralgia, Leucopenia, mild thrombocytopenia. Dengue Hemorrhagic Fever (DHF)is one having above signs along with one or more of be following: positive tourniquet test, Thrombocytopenia < 100,000, Hematocrit rise ≥ 20%, spontaneous bleeding. Dengue Shock Syndrome (DSS) is one having above signs with circulatory failure weak pulse, hypotension, restlessness or Profound shock with undetectable BP and Pulse[3]. WHO classifies dengue into 2 major categories[4]:Dengue (with / without warning signs) and SevereDengue.Dengue fever without warning signs Living in or travel to dengue endemic area presenting with Fever and 2 of the following criteria: Nausea, vomiting, Rash, Aches and pain, positive tourniquet test, Leucopenia, Laboratory confirmed dengue. Dengue fever with warning signsareabdominal pain or tenderness, Persistent vomiting, Clinical fluid accumulation, mucosal.

Bleed, Lethargy, restlessness, Liver enlargement >2cm, Increase inhematocritwith rapid decrease in platelet count[4]. Severe dengue is potentially a fatal complication due to plasma leakage, fluidaccumulation,respiratory distress, severe bleeding, or organ impairmentwhich require close observation to avoid complications and risk of death.Haemopoietic system is the earliest and commonly Affected system with thrombocytopenia being the most common laboratory finding. Possible mechanisms include direct bone marrow suppression by the virus, anti-dengue antibody mediated platelet destruction, effects of cytokine release, peripheral consumption of platelets and Isolated viral replication in the platelet[5]. The virus may be detected by testing NS1antigen and by enzyme-linked immunosorbent assays (ELISA) IgM antibodies appearing 1 week after infection reaching highest at 2 to 4 weeks and remaining detectable for about 3 months and IgG antibody which appear later than IgM remaining for years. The number of dengue cases reported to WHO increased over 8fold over the last two decades, from 505,430 cases in 2000 to over 2.4 million in 2010 and 5.2 million in 2019 with deaths increased from 960 in 2000 to 4032 in 2015. The largest number of dengue cases ever reported globally was in 2019.In India (Karnataka) also number of cases increased from 99913 (5077) with 220 (9) deaths in 2015, to 157315 (16986) cases with 166(13) deaths in 2019[6].The sub-classification of dengue with or without warning signs is designed to help health practitioners to triage patients for hospital admission, ensuring close observation minimizing the risk of developing severe dengue. As thrombocytopenia is one of the laboratory parameter in grading severity, we commonly see positive dengue serology with thrombocytopenia patients being referred as this is a tertiary care referral center with availability of blood products. Hence it is planned to study other warning signs, laboratory parameters with the severity of thrombocytopenia in dengue fever. This study would have a substantial impact on management by reducing morbidity and mortality associated with dengue, reducing unnecessary burden on patients and by reducing referrals' to higher canters.

AIMS AND OBJECTIVES

To study warning signs, laboratory parameters in different age groups, sex, with severity of thrombocytopenia with management.

MATERIAL AND METHODS

It is a prospective observational study conducted for a period of 3 months from November 2019 to January 2020 in the Department of General Medicine, Shridevi institute of medical sciences and research hospital, Tumakuru. All patients admitted with platelet counts less than 1.5 lakh per microliter with laboratory confirmed dengue cases were included in the study. Inclusion criteria: 1. all in patients with Dengue NS1Antigen positive or IgM/IgG positive. 2. Platelet count less than 1, 50,000 per dl. Exclusion criteria 1. Age less than 15 years. 2. Other causes of thrombocytopenia due to infections other than dengue, megaloblastic anemia, cirrhosis etc. Detailed clinical history and detailed physical examination was recorded in a prescribed proforma including age, sex, symptoms like fever, headache, arthralgia, nausea, vomiting, pain abdomen, hematuria, bleeding gums, hematemesis and significant clinical signs like hypotension,

tachypnea, heart rate, mucosal bleed, purpuric spots, tourniquet test, tender abdomen, icterus, hepatomegaly, ascites, splenomegaly, were recorded. All patients were subjected to Dengue NS1Antigen, IgM and IgG antibodies, Complete blood count and analyzed for hemoglobin, hematocrit, leukocyte count and platelet count by Automated Analyzer with confirmation by pathologist for thrombocytopenia by peripheral blood smear, Random Blood Sugar, Urine analysis, Malarial parasite, Widal test, Liver Function tests, Renal Function tests, Abdominal sonography, Chest radiography, ECG, Echocardiography. Patients were managed conservatively with fluid supplementation and platelet transfusion whenever required. Data was entered in Microsoft Office Excel Sheet 2010 and analyzed the results.

RESULTS

During the study period 150 patients are serologically positive for Dengue. Among them 124 had thrombocytopenia, platelet count less than 150000.76 had severe (3300 being lowest in our study with 46 having 10000 to 30000and 37 having 30000 to 50000), 34 had had moderate, and 14 had mild thrombocytopenia (Table No 1).

Table 1. Severity of thrombocytopenia

PLATELET COUNT	NO.OF PATIENTS(124)	PERCENTAGE
100000 -150000 (MILD)	14	11.3%
50000 - 100000 (MODERATE)	34	27.4%
<50000 (SEVERE)	76	61.3%
<10000	01	
10000 - 20000	26	
20000 - 30000	20	
30000 - 40000	17	
40000 - 50000	12	

Among 124, 74(60%) are NS1 positive, 57(46%) are IgM positive, 44 (35%) are IgG positive, 27 (21%) are NS1 and IgM positive, 16(12%) are NS1 and IgG positive, 12(10%) are NS1,IgG,IgM positive(Table 2).

Table 2. Dengue serology report of patients

Dengue serology	No. of patients	percentage
NS1 antigen	74	60%
IgM Dengue	57	46%
Ig G Dengue	44	35%
NS1 antigen + IgM Dengue	27	21%
NS1 antigen + IgG Dengue	16	12%
NS1 antigen+ IgM Dengue + IgG Dengue	12	10%

Among 124 there were 79 males (64%) with 51 severe, 19 moderate,9 mildthrombocytopenia and 45 females (36%) with 25 severe, 15 moderate,5 mildthrombocytopenia(Table 3).

Table 3. Gender distribution of patients

SEX	MALE	FEMALE
MILD THROMBOCYTOPENIA	09	05
MODERATE THROMBOCYTOPENIA	19	15
SEVERE THROMBOCYTOPENIA	51	25
TOTAL PATIENTS	79 64%	45 36%

There were patients from 15 to 70 yearsof age with highest incidence in the age group of 15-30 years in 60 cases followed by 25 cases 31-40 years, 22 in 41- 50 and 17 in51-70 years.Majority (69%) are in 15 to 40 years with 36% in 21-30, 20% in31-40,18% in 41-50, only 5% in >60 years(Table No 4).

Table 4. Age distribution of patients

AGE GROUP	MILD	MODERATE	SEVERE	TOTAL
15 TO 20 YEARS	03	03	09	15 (12%)
21 TO 30 YEARS	04	13	28	45 (37%)
31 TO 40 YEARS	04	06	15	25(20%)
41 TO 50 YEARS	00	08	14	22(18%)
51 TO 60 YEARS	01	03	06	10(08%)
61 TO 70 YEARS	02	01	04	07(05%)
TOTAL CASES	14	34	76	124

The commonest clinical presentation in the study is fever in all followed by Headache in 87, myalgia in 85, nausea and vomiting in 52,arthralgia in 34 patients.The commonest warning signs are abdominal pain in 22,bleeding manifestations in 8, restlessness in 10,altered sensorium in 5 cases. The commonest clinical signs arebradycardia in 33, hypotension in 22, hepatomegaly in 14 cases.(Table No 5).

Table 5. Commonest clinical manifestations with warning signs

CLINICAL MANIFESTATIONS	TOTAL CASES (124)	SEVERE (76) THROMBOCYTOPENIA
HEADACHE	87(70%)	55 (72%)
MYALGIA	85(68%)	50(65%)
NAUSEA/VOMITING	52(41%)	32(42%)
ARHRALGIA	34(27%)	21(27%)
BLEEDING MANIFESTATION	08(06%)	06(8%)
ABDOMINAL PAIN	22(18%)	14(18%)
RESTLESSNESS	10(8%)	07(9%)
BRADYCARDIA	33(26%)	26(34%)
HYPOTENSION	22(17%)	15(20%)
HEPATOMEGALY	14(11%)	11(14%)
ALTERED SENSORIUM	05(4%)	05 (6%)

The commonest abnormallaboratory parameters observed are leucopenia in 53, hematocrit more than 45 in 18, abnormal renal function tests in 25, elevated liver enzymes in 36 andhyperbilirubinemiain 10 cases. (Table No 6).

Table 6. Commonest AbnormalLaboratory Parameters

LABORATORY PARAMETERS	TOTAL (124)	SEVERE (76)
LEUCOPENIA	53(43%)	33 (43%)
HAEMATOCRIT	18(15%)	17(22%)
RENAL FUNCTION TESTS	25(20%)	15(20%)
ELEVATED LIVER ENZYME	36(29%)	27(35%)
HYPERBILIRUBINAEMIA	10(08%)	08 (11%)

There are 124 cases of Dengue Fever out of which 88 are graded as DHF and 22 as DSS. There are 110 Dengue Fever with warning signs having platelet count of less than 1lakh.There are 30 Severe Dengue out of which 22circulatory collapse, 5 neurologiical,10 hepatic and 18 renal damage. (Table No 7).

Table 7.

GRADING OF DENGUE	NO. PATIENTS
Dengue Fever	124
Dengue with warning signs	110
Severe Dengue	30
Dengue Haemorrhagic Fever	88
Dengue Shock Syndrome	22

Platelet transfusion done in 34 cases ofwhich 29 are NS1 /IGM positive.
There wasno mortality in the study.

DISCUSSION

During our study majority 88.7% had platelet count of less than 100000/dl, compared to 86% by shankarappa[7]in a study of thrombocytopenia, 74% by Naveen[8]and 77.2% by Girish [9]in study of dengue fever from same area,77.2% by vidyadar rani [11]from Telangana.11.3% had mild,27.4% had moderate and 61.3% had severe thrombocytopenia compared to 61% by vidyadar rani [11]. During our study 60% NS1 positive,46% IgM positive,21% both NS1 & IgM positivecompared to70% NS1 positive,7% IgM positive, 11% both NS1 & IgM positive by Girish [9], 66.9% NS1 positive, 33.1% NS1&IgM positivebyWayez A[12],33%NS1 positive,63%IgM positive byShivrajNagnathKanthikar[10],49% NS1 positive,5%IgM positive, 3% NS1& IgM by vidyadar rani [11]51% NS1 positive byPattaApparao[13]During our study64% male 36% female compared to 56% male 44% femaleby Naveen [8],59% male 41% femaleby Girish[9], 61.5% males 38.5% females vidyadar rani [11],55% male45% female by Wayez A[12,] 53% male 47% female by Shwetha JH[14]. During our study 49%are in 15-30 age (12% in 15-20, 37% in 21-30), 20% in 31-40age compared to43.52% in15-30by vidyadar rani [11],66% in15-30 by Wayez A[12], 68% in 15-40 by Naveen [8].The commonest clinical presentations along with fever in the study are Headache 70%, myalgia 68%, nausea and vomiting 41%, arthralgia 27%compared to headache 68% myalgia 72%, nausea and vomiting 31%, arthralgia 43% % by Naveen [8],headache 70%, arthralgia 45% by Girish[9].There is no difference among severity of thrombocytopenia. The commonest warning signs are abdominal pain in 18%, bleeding manifestations in 6%, restlessness in 8%, bradycardia in 26%, hypotension in 17%, hepatomegaly in 11% altered sensorium in 4%. Bleeding manifestations, bradycardia, hypotension, hepatomegaly are more common in severe thrombocytopenia. Bleeding manifestations are 13.1% by Wayez A[12],8% by Girish [9]. The commonest abnormal laboratory parameters observed are leucopenia in 43%, abnormal renal function tests in 20%, elevated liver enzymes in 35% cases compared to leucopenia in 27%, abnormal renal function tests in 27%, elevated liver enzymes in 24.5% by Wayez A[12].There are 88% Dengue with warning signs.24% Severe Dengue with 17% circulatory collapse,14% renal, 8% hepatic and 4% neural damage as narrated byNatarajGangasiddaiah[15]. Platelet transfusion done only in 27%.

CONCLUSION

Thrombocytopenia is one of the commonest warning signin dengue fever specially moderate to severe thrombocytopenia in young adults who are serologically NS1 / IgM positive followed by abdominal pain, bleeding manifestations, restlessness, altered sensorium,leucopenia. Cardiovascular warning signs likebradycardia, hypotension, polyserositis, Hepatic warning signs like abdominal tenderness, hepatomegaly, elevated liver enzymes, hyperbilirubinemia, Renal warning signs likeabnormal renal function tests and Neurological warning signs like altered sensoriumare commonly observed. Dengue fever with thrombocytopenia is one of the most common important major public problem in India where cyclic epidemics are becoming more frequent.Majority require supportive management and maynot require platelet transfusion. Most of the cases can be managed at the local hospital with close monitoring of warning signs and laboratory parameters. Early recognition of warning signs and meticulous management can reduce the morbidity and mortality of dengue.

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