Original Research Paper

Pathology

THE UTILITY OF TOTAL LEUCOCYTE COUNT IN DENGUE

Saurabh Shrivastava

Ramveer Rajput*   *Corresponding Author

ABSTRACT

Background: Dengue infections are public health concerns in India, where they occur in epidemics and have a high mortality in the advanced stages. Clinical features are nonspecific, and diagnosis is supported by lab features. One of these lab tests include total leucocyte count-easily available, simple and cost effective which is useful in small rural set ups for early diagnosis and prognosis of dengue. Leucopenia is caused by bone marrow suppression by virus in acute phase and is due to decrease in polymorphs. The aim of this study is to analyse the importance of total leucocyte count patterns in dengue and assess its utility as early marker of dengue and prognostic indicator of severe dengue.

Methods: A total of 82 serologically proven cases of dengue with total white cell counts (blood counts obtained by 3 part Automated hematology analyser & correlated with peripheral smear) during 6 months from May to November 2018 were analysed.

Results: In our study, most cases were noted in the younger age group with a male predominance. The range of total leucocyte count was 0.8x109/l to 13.6x109/l. Most (42.7%) had leucopenia, normal counts was noted in 39%. 57.1% had mild leucopenia, 51.4% of leucopenia cases were associated with severe thrombocytopenia. 51.4% of leucopenia cases were NS1 positive while only 17.2% were antibody positive.

Conclusions: Total leucocyte count is one of the simple, easily available, cost effective tests useful in small rural set ups for early diagnosis and prognosis in dengue and helps reduce the morbidity and mortality of dengue.

KEYWORDS : Dengue fever, Leucopenia, Lymphocytosis, Thrombocytopenia

INTRODUCTION

Dengue, an arboviral infection (DENVI-4) is transmitted by Aedes mosquito.[1] The clinical manifestations include headache, fever, retro orbital pain, myalgia, body pain, rash.[2] Dengue has been included as an emergent public health issue with 50 million infections annually, with 40% of population at risk in tropics and subtropics.[3]

In India, epidemics are frequent, straining the limited resources of public health system. Dengue is mostly self-limiting, but mortality from complications can be about 20% if untreated.[5] Dengue presents with a wide clinical spectrum which includes undifferentiated fever, Classic Dengue, Dengue Hemorrhagic Fever and Dengue Shock Syndrome.[2]

It may be confused with other febrile illnesses like Malaria, Typhoid, Leptospirosis, Chikungunya, Cox sackie, Infectious Mononucleosis, Rickettsia, Rubella, Influenza etc. So, clinical diagnosis in early phase is difficult.[6-9] However, early rapid diagnosis is important in-patient management as currently there is no specific treatment or vaccine available for dengue.[8] In clinical practice, diagnosis is based both on clinical features and lab tests.[10] Serological tests, confirm dengue late in the course of the disease.[11] Simple hematological parameters not only help in early diagnosis of dengue but also can predict onset of severe dengue and are useful in smaller rural setups with limited resources.[12,13] The hematology tests of importance are platelet counts, total leucocyte count and hematocrit.[7,12] However changes in platelet count and hematocrit occur in later stages of infection, after 3rd - 4th day.[9,14] The earliest hematological abnormality in dengue is a progressive decline in white cell counts.[15-17]

Leucopenia, defined as total leucocyte count <4x109 /l is a prominent and supposedly the second most common feature in dengue.[9,18] It gives enough clue for diagnosis of Dengue and helps in differentiation from other febrile illnesses thus aiding in reducing its morbidity and mortality.[12,19,20] Some studies have observed that total leucocyte counts/leucopenia could serve as a prognostic factor for dengue severity while others dispute it.[10,13-17,21,22]

A few studies have observed that there is a progressive decline in white cell counts with sudden platelet drop which precedes plasma leakage and hence it could be the earliest prognosticator of severe dengue.[23] Our study focuses on the significance and patterns of one such simple, routine test the total white cell count in diagnosis of dengue. The aim of the study is to analyse the total white cell count patterns in dengue, assess its role in diagnosis and utility as early marker of dengue infection and prognosticator of severe dengue.

METHODS

This is a Retrospective study done on 82 patients with positive dengue serology in Sunrise Diagnstic Lab, Gwalior, M.P., over a 6 month period from May to November 2018. All patients with serological confirmation of dengue (NS1 /IgM/IgG/ positivity) done by ELISA method with Total leukocyte counts along with hematocrit, differential leucocyte count, and platelet count were included in the study.

Exclusion criteria Patients with concomitant infections like malaria, typhoid etc. along with Dengue and patients with normal or increased platelet count.

The hematological data (obtained from 3 part Automated hematology Analyser) of these cases was tabulated for analysis. The differential leucocyte count was done on peripheral blood smears stained by Leishman's stain (done for confirmation of platelet counts as per protocol).

RESULTS

A total of 82 dengue serology positive cases were analyzed. It showed an age range between 9 months to 60 years, the average being 29 years. The majority of patients were in the 8-25 years group. There were 57.3% of cases above 14 years and 42.7% of cases below 14 years (Table 1).

Table 1: Age wise distribution of patients.

Age group	Number of cases (n=82)	Percentages (%)
Adults*(above 14 years)	47	57.3
Pediatric (below 14 years)	35	42.7

Males predominated over females with a male to female ratio of 1.6 :1 (Table 2).

Table 2: Gender wise distribution of patients.

Gender	Number of cases (n=82)	Percentages (%)
Males	51	62.2
Females	31	37.8

An analysis of white cell count in our study showed a range between 0.8x109/l to 13.6x109/l. (Table 3).

Table 3: Total white cell count distribution.

Total white cell count	Number(n=82)	Percentages (%)
< 4 x 109 /l	35	42.7
4-11 x 109 /l	32	39.0
> 11 x 109 /l	15	18.3

Age and gender distribution patterns in leucopenia is summarized in Table 4.

Table 4: Age and gender distribution in patients with leucopenia.

Gender	Adults			Pediatric		
	Total	Number of cases with leucopenia	(%)	Total	Number of cases with leucopenia	(%)
Males	28	11	39.3	23	10	43.5
Females	19	08	42.1	12	06	50.0
Total	47	19	40.4	35	16	45.7

Leucopenia was graded as mild, moderate, severe. It was noted that majority of cases showed mild leucopenia (57.1%). (Table 5).

Table 5: Degree of leucopenia.

Grade (x 10^9/l)	Number (n=35)	(%)
Mild (2 to 3.999 x 10^9/l)	20	57.1
Moderate (1-1.999 x 10^9/l)	14	40.0
Severe ($\leq$ 0.999 x 10^9/l)	01	2.9

An analysis of leucopenia with thrombocytopenia was done. A total of 35 cases had leucopenia in association with thrombocytopenia. Thrombocytopenia was graded as mild with platelet counts between 76-150x10^9/l, moderate with counts between 50-75x10^9/l and severe with counts less than 50x10^9/l. Almost over half the cases (51.4%) showed severe thrombocytopenia in association with leucopenia. 28.6% showed moderate thrombocytopenia in association with leucopenia. (Table 6).

Table 6: Leucopenia and degree of thrombocytopenia.

Degree of thrombocytopenia (x109/l)	Number of cases with leucopenia (n=35)	(%)
Mild (76-150 x 10^9/l)	07	20.0
Moderate (50-75 x 10^9/l)	10	28.6
Severe (<50 x 10^9/l)	18	51.4

We also analysed leucopenia with serology. It was noted that almost half of the leucopenia (51.4%) cases were significantly associated with isolated NS 1 positivity in serology and 82.8% showed NS 1 with antibody association. Serology pattern in leucopenia is shown in table 7.

Table 7: Serology patterns in leucopenia.

Serology pattern	Number (n=35)	(%)
Ns1 alone	18	51.4
Ns1 with IgG/IgM/both	11	31.4
IgG/IgM only	06	17.2

DISCUSSION

Our study analyzing age was in concordance with others with most cases in the younger ages with slight male predominance probably due to occupational exposure and increased recreational activity in men.[18,21] An analysis of white cell counts showed a range of 0.8x10^9/l to 13.6x10^9/l, in accordance with other studies.[2,7] Leucopenia (<4 x10^9/l) was noted in 42.7% in accordance with other studies.[7,11,12,17,21] A few studies used a threshold of <5x109/l for leucopenia.[23,24] A few studies had a lower and others, a higher proportion of cases with leucopenia.[1,2,4,15,16,18,25] A normal leucocyte count was observed in 39% of cases in our study in concordance with few studies but it was lower and higher in other studies.[2,4,15,18,21,24]

Leucocytosis was noted in 18.3% of cases in our study in concordance with few studies.[25] It was seen in lower and higher proportion of cases in other studies.[15,18,21]. A demographic assessment of leucopenia revealed an equal distribution of cases across the ages and both sexes. Francisca et al and Thanachartwet et al noted increased risks of leucopenia in the ages $\geq$15 years. We had no data to compare these findings.

Our analysis of the degree of leucopenia showed most (57.1%) cases with mild leucopenia. Severe leucopenia was noted in 2.9%[18,21].

A few studies of the total and differential leucocyte count patterns have observed mild initial leucocytosis accompanied by neutrophilia followed later by leucopenia and lymphocytosis with atypical lymphocytes.[10,22]

Few studies claim that leucopenia with lymphocytosis is a major finding in dengue.[12]

Vibha et al have also observed that leucocyte count returns to normal by 9th-10th day post therapy and is an important benchmark for clinical improvement.

Leucopenia is caused by bone marrow suppression by virus in acute phase and is due to decrease in polymorphs.[7,17,18,20,25] Neutropenia is also attributed to marked degeneration of mature neutrophils in febrile phase with shift to left.[21] Stress accompanied with shock may be the cause of mild initial leukocytosis.[10]

A few studies claim positive correlation between leucopenia and thrombocytopenia which is not statistically significant.[16,17] In their study Juan Carlos et al have observed that leucopenia is accompanied by a sudden drop in platelet count preceding plasma leakage. Our study suggests that leucopenia could be a marker of severe dengue as over half (51.4%) of the cases are associated with severe thrombocytopenia. Few studies claim that leucopenia indicates good prognosis with counts >4x10^9/l being associated with severe dengue.[10,13,14] Vibha et al noted that leucopenia is commoner in Dengue fever, Dengue hemorrhagic fever I/II but not in Dengue shock syndrome.

An analysis of serology patterns with respect to leucopenia showed that 82.8% of leucopenia cases were NS1 positive as against 17.2% of leucopenia cases which had antibody only (IgM/IgG) positivity. A few studies showed mean total leucocyte count was lower in those with NS 1 positivity compared to (IgM/IgG) antibody positivity.[27]

The analysis of leucopenia cases associated with serology patterns showed that 51.4% NS1 positive cases whereas 17.2% antibody only (IgM/IgG) positive cases had leucopenia. This was in accordance with other studies.[3,28]

NS 1 antigen is known to be a marker for early diagnosis of the disease and is detected from first day, followed by IgM at 3-5 days and IgG from 1st week onwards.[27,29,30]

A few studies analysing thrombocytopenia with serology patterns also have observed a higher proportion of cases with thrombocytopenia in NS 1 positivity than with antibody positivity.[29]

CONCLUSION

Early diagnosis is crucial to the management of dengue and helps in reduction of morbidity and mortality. Total leucocyte count is simple, easily available, cost effective test, very useful in small rural set ups with limited resources; not only for early diagnosis but also for prognosis in dengue. Leucopenia is an early marker of dengue and association of leucopenia with thrombocytopenia suggests that it could be one of the prognosticator of severe dengue.

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