Clinical profile & Laboratorial trend of Thrombocytopenia in Dengue fever

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ABSTRACT

Introduction : Amongst the various causes of febrile thrombocytopenia, Dengue carries more morbidity and mortality. Its manifestations are varied, from mild febrile illness to bleeding diathesis, multi-system involvement and shock. This study was carried out to profile the clinical presentation, complications and thrombocytopenia trends in Dengue and compare it with the non- Dengue patients.

Methods : Consecutive patients with fever and thrombocytopenia were included in the study. Thorough clinical examination and laboratorial investigations (CBC, LFT, KFT, chest X-Ray, USG abdomen) were done in all patients.

Results : 60 patients (29 Dengue and 31 non - Dengue) were included. Symptoms like retro-orbital pain, headache and vomiting ($p < 0.05$) and investigations like raised transaminases, GB wall edema, abnormal chest X-Ray and ascites were significantly more in Dengue patients. The mean platelet counts on day 1 and 3 were significantly lower and the day 1, 3 and 5 haematocrit was significantly higher in the Dengue group ($p < 0.05$). 3 (10.34%) patients had bleeding tendencies and 4 patients received platelet replacement therapy, all were from the Dengue group. There was no mortality in either group.

Conclusion : Amongst the patients with febrile thrombocytopenia, retro-orbital pain, headache, vomiting, transaminitis, hemoconcentration, gall bladder wall edema and plasma leak in the form of ascites and pleural effusion is more likely to predict Dengue. Thrombocytopenia is more severe and bleeding tendencies were more frequent in Dengue patients.

Key words : Febnle thrombocytopenia, Dengue Fever.

Introduction :

First reported in 1780, when Benjamin Rush described this condition as "break bone fever," Dengue is a mosquito borne viral infection of genus Aedes, principally Aedes aegypti[1]. In India, the first major epidemic illness clinically compatible with dengue was reported from Madras in 1780, which later spread all over the country.[2] Annually, an estimated 390 million Dengue infections occur every year (95% credible interval 284-528 million), of which 96 million (67-136 million) manifest clinically (with any severity of disease).[3] In India, there has been an exponential rise in the number of Dengue patients in recent years.

The spectrum of illness caused by the virus includes Dengue fever (DF), Dengue hemorrhagic fever (DHF), and Dengue shock syndrome (DSS). Though certain features of Dengue like headache, myalgia, arthralgia, rash, and thrombocytopenia may simulate other viral illnesses, what differentiates Dengue is its propensity for complications in its 'Expanded' spectrum causing multi-system manifestations, bleeding diathesis, life - threatening 'capillary leak syndrome' and shock[4,5].

Transient thrombocytopenia is a common occurrence in Dengue and is attributed to immune destruction, bone marrow suppression and platelet aggregation to virus infected endothelium[6]. Drop in platelet counts may herald the capillary leak syndrome characterized by hemoconcentration and plasma leakage in the third space. Thrombocytopenia, along with coagulopathy, contributes to the bleeding tendencies in Dengue and may necessitate transfusion (platelet / FFP / blood) therapy.

The present study was carried out to study the clinical manifestations, platelet trends and outcome of all confirmed dengue cases admitted in a tertiary care Hospital in a rural set-up.

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Methods :

It was a hospital-based case control study. The study was initiated after approval from IEC. The information was collected using a preformed semi-structured questionnaire. Sixty patients admitted with fever and thrombocytopenia, during one month period from 1st October to 1st November 2017 were included in the study. Patients with known platelet disorders, chronic liver disease or drugs causing thrombocytopenia were excluded.

Detail clinical examination of all patients was done on inclusion in the study. This included the symptoms (fever, headache, myalgia, bleeding manifestations) and signs ((warning signs of dengue fever, signs of haemorrhage, signs of plasma leakage and signs of shock).) Laboratory investigations such as Hemoglobin, total count, differential count, platelet count, packed cell volume, peripheral smear for malaria parasite, liver function tests and renal function test were done in all patients. Serological test for dengue fever (NS1, IgM, IgG) and radiological investigations such as X-ray chest and USG abdomen were done in all patients. Abnormalities on chest X-ray like pleural effusion, heterogeneous opacities suggestive of pneumonitis were noted. USG abdomen was done to see for ascites (as a measure of capillary leak) and gall bladder wall edema. Other investigations such as Urine examination, Widal test, blood culture etc were done in appropriate clinical settings. Haematocrit was done as a measure of capillary leak.

To determine the trends and recovery of haematocrit and platelet count, these were done serially on days 1, 3 and 5. Day of admission was considered as day 1. Patients with positive Dengue serology (NS1 and / or IgM) were considered as cases; patients with negative Dengue serology acted as controls. Patients were assessed daily and followed up till the entire duration of hospital stay.

All Dengue patients were managed according to the standard protocol. Platelet replacement therapy in the form of platelet concentrate or single donor Platelet (SDP) was given according to recommendations (Symptoms / signs of mucosal bleed / prophylactically if Platelet count < 10,000 / microliter).

Statistical Analysis :

The calculated sample size was 60 (convenient samplings). Data was collected and compiled using EPI Info 7.2. The qualitative variables were expressed in terms of proportions and the difference between two proportions was tested by chi square or fisher exact test. The quantitative variable were either categorized and expressed in percentages or expressed in terms of mean and standard deviation. The difference between two means was tested by t test. All analyses were two tailed and significant level was set at 0.05.

Results :

Total 60 patients satisfying the inclusion criteria were included in the study. There were 29 cases and 31 controls. Most (86.5% of cases and 76.74% of controls) patients in both the groups were young, in the age group 20-40 years. There was male preponderance in both the groups; however the age and gender distribution did not show any significant difference in the cases and controls. There was no significant difference in the duration of fever before admission. Thus the cases and controls were comparable with respect to the age, gender and the duration of fever ***(Table 1)***.

Table 1 : **Showing distribution of patients according to the duration of fever on admission**

Duration of Fever (days)	**Dengue**		**Non-Dengue**		**Total**		**p-value**
	Number	**%**	**Number**	**%**	**Number**	**%**	
0-5	16	55.17	16	51.61	32	53.33	0.1093
5-10	11	37.93	7	22.58	18	30.00	
>10	2	6.90	8	25.81	10	16.67	
Mean	4.62		5.35		5.00		0.3907
SD	2.90		3.66		3.30		

Of the 29 cases, 3 patients had hemorrhagic tendencies and 1 presented with shock; the rest had classical Dengue fever. On comparing the clinical features between the two groups, statistically significant difference was observed for symptoms like retro- orbital pain, headache and vomiting ($p < 0.05$) whereas both the groups were comparable for the pulse rate and mean systolic as well as diastolic blood pressure ($p > 0.05$). 3 of the 29 cases (10.34%) had bleeding manifestations (symptoms and/or signs) whereas none of the controls had any bleeding manifestations. However the difference was not statistically significant ($p = 0.1067$).

Amongst the laboratory investigations, both SGOT and SGPT were significantly elevated in the cases as compared to the controls ($p = 0.001$ and $p = 0.0001$ respectively). Similarly abnormal chest X-Ray and ascites were commoner in cases as compared to controls; the difference was statistically significant ($p = 0.0487$). More Dengue patients had gall bladder wall edema on USG than the non- Dengue patients and the difference was statistically significant ($p = 0.001$) ***(Table 2)***.

The mean platelet levels on day 1 as well as day 3 were significantly lower in the cases as compared to the controls. In both, the cases and controls the

Table 2 : **Showing distribution of patients according to the clinical features and investigations**

Gender	Dengue		Non-Dengue		Total		p-value
	No / Mean	%	No / Mean	%	No / Mean	%	
Retro-orbital pain	29	100	2	6.45	31	51.67	<0.001*
Headache	29	100	8	58.06	47	78.33	<0.001*
Vomiting	21	72.41	4	12.90	25	41.67	<0.001*
Bleeding Tendencies	3	10.4	0	0	3	5.00	0.1067
Pulse rate (Beats/min)	93.28	12.42	92.33	6.07	92.73	9.60	0.6827
SBP (mm Hg)	110.41	9.70	112.52	4.93	111.50	7.62	0.301
DBP (mm Hg)	72.55	6.67	75.10	5.03	73.87	5.97	0.5336
SGPT (IU/L)	103.34	52.67	50.68	46.62	76.13	55.91	0.0001*
SGOT (IU/L)	112.86	65.91	40.87	27.44	75.67	61.33	<0.001*
Abnormal Chest X Ray	4	13.79	0	0	4	6.67	0.0487*
USG GB wall Edema	25	86.21	0	0	25	41.67	<0.001*
USG -Ascites	4	13.79	0	0	4	6.67	0.0487*

SBP - Systolic blood pressure, DBP - Diastolic blood pressure, USG - Ultrasonography, *Significant p-value

Table 3 : **Showing platelet trends in Dengue Vs non Dengue patients**

Platelet count (per micro liter)	Dengue		Non-Dengue		Total		p-value
	Mean	SD	Mean	SD	Mean	SD	
Day 1	0.80	0.66	1.73	0.64	1.28	0.80	<0.001*
Day 3	0.79	0.67	1.30	0.61	0.92	0.68	0.0399*
Day 5	1.07	0.55	1.22	0.55	1.09	0.54	0.6102

*Significant p-value

Table 4 : **Showing PCV (Haematocrit) Trends**

Hamatocrit (percentage)	Dengue		Non-Dengue		Total		p-value
	Mean	SD	Mean	SD	Mean	SD	
Day 1	44.30	6.01	40.39	6.06	42.28	6.30	0.0148*
Day 3	43.91	4.20	40.08	5.40	42.93	4.77	0.0267*
Day 5	43.27	4.28	33.66	20.63	41.67	9.33	0.0330*

*Significant p-value

platelet levels dropped further on the third day before showing an incremental trend. The day 3 fall in the mean platelet level was more in non - Dengue patients but the rise on day 5 was more in the Dengue patients ***(Table 3).*** On day 1 the haematocrit in the cases was significantly more than the controls (p = 0.0148). Though the haematocrit showed a decremental trend in the cases on day 3 and 5, it continued to be higher than the controls, the difference being statistically significant ($p < 0.05$) ***(Table 4).***

There was no statistically significant difference in the duration of hospital stay between the two groups (p = 0.1487) ***(Table 5).*** In the present study, 4 patients were treated with platelet replacement therapy. All 4 patients had platelet count below 50,000 / microliter and were from the Dengue group (p = 0.0487). Of these, 3 patients had active mucosal bleed whereas the fourth patient was given prophylactic platelet transfusion as the platelet count was 6000 / microliter. None of the controls received platelet transfusion ***(Table 6).*** There was no mortality in the present study population.

Discussion :

The present study was carried out to document the clinical profile, laboratorial trend of thrombocytopenia and short term outcome in Dengue as compared to non-Dengue. There was male preponderance and most patients were young, in the age group 20-50 years. Manoj C M[7], Seema et al[8], Karoli et al[9], Jain et al[10] and Patil et al[11] also made similar observations.

The study was carried out in the month of October and November, a period during which we get to see many patients of febrile thrombocytopenia. The different causes of febrile thrombocytopenia, besides Dengue, include other infections (Malaria, other viral infections like EBV, CMV, Rubella, etc, sepsis), or haematological conditions (malignancies, aplastic anemia, ITP, DIC etc).[12] However the present study, like previous other studies[12,13] revealed that the symptoms like retro-orbital pain, headache and persistent vomiting are more likely to be found in Dengue. Thus presence of these symptoms may prompt the clinician to suspect Dengue. Early diagnosis and prompt institution of appropriate management may, in turn improve the outcome.

The clinical profile of Dengue, described as Expanded Dengue includes a wide spectrum of manifestations including CNS, GIT, CVS, renal and haematological involvement[4,5]. The hepato-biliary involvement varies from asymptomatic 'Transaminitis' to acute liver failure[5,7,12,14]; elevation in SGOT levels is more than those in SGPT levels[5,14,15] as has been seen in the present study.

Table 5 : **Showing duration of hospital stay**

Duration of hospital stay(days)	Dengue		Non-Dengue		Total		p-value
	No	%	No	%	No	%	
0-5	11	37.93	12	38.71	23	38.33	
5-10	15	51.72	19	61.29	34	56.67	
>10	3	10.34	0	0	3	5.00	0.1781
Mean	5.66		4.61		5.12		
SD	3.45		1.61		2.69		

Table 6 : **Showing distribution of subjects according to platelet replacement therapy**

Platelet concentrate / SDP therapy	Dengue		Non-Dengue		Total		p-value
	No	%	No	%	No	%	
Yes	4	13.79	0	0	4	6.67	
No	25	86.21	31	100	56	93.33	0.0487*
Toatal	29	100	31	100	60	100	

*Significant p-value

The commonest rhythm disturbance seen due to CVS involvement in Dengue is sinus bradycardia followed by sinus tachycardia, ventricular ectopy and first degree heart block[16]. Transient myocarditis manifesting as sinus tachycardia, STT changes on ECG or myocardial pump failure have also been described[5]. In the present study the mean pulse rate in cases, though slightly higher, was not significantly different from that in the controls. Other CVS complications have not been observed.

Significantly more Dengue patients had radiological evidence of plasma leak on chest X Ray and Ultrasound (13.79% each). Similarly, Fujimoto[15] observed ascites in 4.7% and pleural effusion in 3.6% patients; Kumar C H[7] described plasma leakage in 20% patients. Deshwal[6] also observed ascites in 16.3% and pleural effusion in 20% of study subjects. The 'leakage' phase is critical in Dengue pathogenesis, characterized by plasma leakage in the third space. The phase coincides with the drop in the platelet count; immune mediated destruction of platelets as well as RBCs and WBCs releases cytokines which activate the complement system triggering the increased capillary permeability. The degree of capillary leak seems to be proportional to the amount of platelet destruction[17].

The capillary leak is also responsible for the rise in haematocrit. Vishnuram et al 12 have observed positive correlation between drop in platelet count and rising haematocrit. However the present study did not find such an association. Moreover, with a drop in the mean platelet counts on day 3, the haematocrit also dropped, though it continued to be higher than that in the controls. Since there was no overt massive bleeding in any of the study subjects, the drop in haematocrit can be attributed to the treatment given to the patients. Serial estimation of haematocrit has been recommended as an important management tool, a rising haematocrit indicating continued capillary leak and adverse prognosis. In fact, haematocrit monitoring (as a surrogate marker of the 'critical phase') can act as an effective alternative for serial platelet estimation as it can avoid unnecessary platelet replacement therapy.[18]

Finally, all patients receiving platelet replacement therapy belonged to the Dengue group (4 out of 29, 13.79%); none from the control group needed it. The difference was found to be statistically significant (p=0.0487). Thus amongst the patients with febrile thrombocytopenia, bleeding tendencies and its therapy is more likely to occur in the Dengue patients as compared to non - Dengue patients. The proportion of patients needing platelet replacement therapy varies from 6.9% to 42.67%[15,19,20]. Thrombocytopenia alone does not seem to be responsible for the bleeding tendencies in Dengue as studies have not shown correlation of platelet count with bleeding tendencies[7,21]. Role of activated fibrinolytic system along with thrombocytopenia and prolonged APTT has been described[22].

Conclusion :

In this hospital based study comparing the clinical and thrombocytopenia profile of Dengue and non-Dengue patients, retro-orbital pain, headache and vomiting were found to be significant clinical predictors of Dengue. Also Dengue patients were more likely to have transaminitis, gall bladder wall edema and plasma leak in the form of Ascites and pleural effusion. Thrombocytopenia was more severe and bleeding tendencies were more frequent in Dengue patients. Similarly haematocrit was higher in Dengue patients indicating capillary leak. Finally, Dengue patients needed platelet replacement therapy thus corroborating the fact that thrombocytopenia in Dengue may be more dangerous and hence a vigilant approach to early diagnosis and management is needed to improve the outcome of these patients.

References :

1. Guzmán MG, Kourí G; Dengue : An update. Lancet Infect Dis. 2002; 2: 33-39.
2. Chaturvedi UC, Nagar R, Shrivastava R. Macrophage and dengue virus : Friend or foe? Indian J Med Res. 2006;124:23-40.
3. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL et.al. The global distribution and burden of dengue. Nature. 2013; 496:504-7.
4. World Health organization Comprehensive guidelines for prevention and treatment of dengue and dengue hemorrhagic fever. New Delhi : WHO, SEARO; revised and expanded edition.
5. Kadam DB, Salvi S, Chandanwale A. Expanded Dengue. JAPI 2016; 64:59-63.
6. Deshwal R, Qureshi MI, Singh R. Clinical and Laboratory Profile of Dengue Fever. JAPI 2015; 63:30-32.

7. Kumar CM, Keerthi Vyas KS, Sai Krishna Y. Clinical profile of dengue fever with severe thrombocytopenia and its complications : a retrospective study at a tertiary care hospital in South India. International Journal of Research in Medical Sciences 2017; 5(5):1751-1755.
8. Seema A, Singh V, Kumar S, et al. The Changing Clinical Spectrum of Dengue Fever in the 2009 Epidemic in North India. J. Clin. Diag. Res., 6: 999-1002.
9. Karoli R, Fatima J, Siddiqi Z, et al. 2012. Clinical profile of dengue infection at a teaching hospital in North India. J. Infect. Dev. Ctries 2012; 6: 551-4.
10. Jain P, Kuber D, Garg AK, Sharma GD, Agarwal AK. Manifestations of dengue fever : A hospital based study. JIACM, 2015. 16(3-4): 204-8.
11. Patil AA. Clinico-laboratory profile of suspected dengue patients in a tertiary care hospital. Medplus Int. Med. J. 2015; 2: 54-7.
12. Vishnuram P, Natarajan K, Karuppuswamy N, Karthikeyan S, Kiruthika J, Muruganathan A. Evaluation of febrile Thrombocytopenia cases in a South Indian Tertiary Care hospital. JAPI 2018;66:61-64.
13. Gupta AK, Peshattiwar P, Romday R, Bhambani P. A Study of Clinical and Laboratory Profile of Dengue Fever cases in a Tertiary Care Teaching Hospital. Int.J.Curr.Microbiol.App.Sci (2016) 5(12): 295-307.
14. Lee LK, Gan VC, Lee VJ, et al. Clinical relevance and discriminatory value of elevated liver aminotransferase levels for dengue severity. PLoS Negl Trop Dis 2012; 6:e1676.
15. Fujimoto DE, Koifman S. Clinical and laboratory characteristics of patients with dengue hemorrhagic fever manifestations and theirtransfusion profile. Brazilian Journal of Hematology and Hemotherapy. 2014; 36(2):115-120.
16. Yadav RK, Kumar S. To study cardiac manifestations in patients pre senting with dengue infection and to find out the correlation of cardiac manifestations to warning signs of dengue. Int J Adv Med. 2017; 4(2):323-328.
17. Biswas T. Capillary Leak Syndrome is Inversely Related to Platelet Count in Dengue. JMSCR 2016;4(9):12315-12320.J
18. Pallavi P, Ganesh CK, Jayashree K, Manjunath GV. Unfurling the Rationale use of Platelet Transfusion in Dengue Fever. Indian J Hematol Blood Transfus. 2011; 27:70-4.
19. Chuansumrit A, Phimolthares V, Tardtong P, Tapaneya-Olarn C, Tapaneya-Olarn W, Kowsathit P, et al. Transfusion requirements in patients with dengue hemorrhagic fever. Southeast Asian J Trop Med Public Health. 2000; 31:10-4.
20. Makroo RN, Vaina V, Kumar P, Kanth RK. Role of platelet transfusion in the management of dengue patients in a tertiary care hospital. Asian J Transfus Sci. 2007; 1:4-7.
21. Raikar SR, Kamdar PK, Dabhi AS. Clinical and laboratory evaluation of patients with fever with thrombocytopenia. Indian J Clin Pract. 2013; 24:360-3.
22. Trzeciak-Ryczek A, Tokarz-Deptu³a B, Deptu³a W. Platelets an important element of the immune system. Polish J Veter Sci. 2013; 16(2):407-13.