Research Article

Coagulopathy in dengue fever patients

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ABSTRACT

Background: The study was done to find out the prevalence of coagulopathy in Dengue fever patients with thrombocytopenia and its clinical significance.
Methods: The patients admitted in medical wards and ICU were included in the study after considering certain inclusion and exclusion criteria. APTT, PT & D-dimer assays were also done in the study population. Coagulopathy was considered when APTT values were ≥41seconds.
Results: 22.3% of the study population showed evidence of coagulopathy. Bleeding manifestations significantly increased with increasing APTT values. There is also significant association between platelet counts and bleeding manifestations. As platelet count falls there is a tendency for APTT to rise.
Conclusion: In addition to thrombocytopenia, coagulopathy also contribute to the presence of bleeding manifestations in dengue fever patients. There is a significant correlation between bleeding manifestations with abnormal APTT values. As platelet count decreases there is tendency for rise in APTT values.

Keywords: Dengue fever, Thrombocytopenia, Coagulopathy, Bleeding manifestations

INTRODUCTION

Dengue is a systemic viral infection transmitted between humans by mosquitoes. It is a self-limiting illness. With more than one-third of the world's population living in areas at risk for infection, dengue virus is a leading cause of illness and death in the tropics and subtropics. The global burden of dengue is large; an estimated 50 million infections per year occur across approximately 100 countries, with potential for further spread.[1]

Dengue Fever (DF) is characterized by fever, headache, muscle or joint pain, and rash. In some cases, however, patients develop the life-threatening complication, Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). Present evidence suggests that haemorrhage in DHF/DSS is related to multiple factors that include thrombocytopenia, coagulopathy, and vasculopathy. In our study we tried to find out the prevalence of coagulopathy in DF patients having thrombocytopenia and its clinical significance.

METHODS

The study was done in a tertiary care centre in South India. Patients admitted to medical wards and ICU were included in the study.

Inclusion criteria were 1. Confirmed DF cases either by positive Dengue NS1Ag or by Dengue IgM results. 2. Patients with thrombocytopenia at the time of admission

(platelet count <150000/mm^3). 3. Patients with normal Packed Cell Volume (PCV) values (high PCV values can interfere with APTT values).

Exclusion criteria were 1. Patients with high PCV values. 2. Patients with underlying cirrhosis or any underlying bleeding or coagulation disorders. 3. Patients with fever and thrombocytopenia who are serologically negative for Dengue. 4. Dengue fever patients with normal platelet count.

Those patients who were included in the study group were monitored for bleeding manifestations. Activated Partial Thromboplastin Time (APTT) and Prothrombin Time (PT) were done in the study population as part of routine investigations.

Those with prolonged APTT values were again subjected to mixing studies with normal plasma for normalisation of APTT. D-dimer assay was done in those patients with persistently abnormal APTT values even after mixing studies.

Coagulopathy is considered when APTT values were ≥41 seconds. APTT values ≤40 were considered as normal. Mixing studies were done only in patients with presence of coagulopathy.

RESULTS

Out of the 264 patients included in the study, 72 (27.3%) patients had bleeding manifestations. Bleeding manifestations were absent in 192 (72.7%) patients. Presence of coagulopathy (APTT ≥41 sec) was present in 59 (22.3%) patients. 205 (77.7%) did not show any evidence of coagulopathy. Prothrombin time was normal in all the patients.

Table 1: APTT vs. bleeding manifestation.

APTT		Bleeding manifestation		Total
		No	Yes	
<36 sec	Count	115	21	136
	% within APTT	84.6%	15.4%	100.0%
36-40 sec	Count	48	21	69
	% within APTT	69.6%	30.4%	100.0%
41-45 sec	Count	16	15	31
	% within APTT	51.6%	48.4%	100.0%
46-50 sec	Count	9	8	17
	% within APTT	52.9%	47.1%	100.0%
51-55 sec	Count	2	2	4
	% within APTT	50.0%	50.0%	100.0%
>55 sec	Count	2	5	7
	% within APTT	28.6%	71.4%	100.0%
Total	Count	192	72	264
	% within APTT	72.7%	27.3%	100.0%

In our study APTT of each patient was checked, and was arranged into a categorical data of 6 groups, with group 1 being the lowest APTT count and group 6 being the highest APTT count (Table 1). When cross tabulated with bleeding manifestation, it was found by Pearson Chi-square, that P value was <0.001. This suggests that bleeding manifestation significantly increased with increasing APTT values.

The APTT values were then categorised as normal (≤40 seconds) and abnormal (≥41 seconds) and then compared for the presence of bleeding (Table 2). The result was highly significant with a P value of <0.001. This also suggests that abnormal APTT values are associated with significantly increased risk of bleeding manifestations

Table 2: Bleeding manifestation vs. APTT.

Bleeding		APTT		Total
		Normal (≤40 sec)	Abnormal (≥41 sec)	
Yes		42	30	72
	%	58.3%	41.7%	100.0%
No		163	29	192
	%	84.9%	15.1%	100.0%
Total	Count	205	59	264
	%	77.7%	22.3%	100.0%

Mixing studies with normal plasma were done in the 59 (22.3%) patients with abnormal APTT values. In this group, APTT values normalised after mixing study in 52 (88.1%) patients whereas remaining seven (11.9%) patients continued to have abnormal APTT values (Table 3). Chi-Square analysis of this data showed no statistical correlation in the prevalence of bleeding manifestation in these two groups (P >0.05). All the seven patients with persistently elevated APTT values even after mixing studies had elevated D-dimer values.

Table 3: Prevalence of bleeding manifestation vs. APTT values after mixing study.

Given FFP		Bleeding manifestation		Total
		Yes	No	
Returned to normal		26	26	52
	%	50.0%	50.0%	100.0%
Continued to be abnormal		4	3	7
	%	57.1%	42.9%	100.0%
Total		30	29	59
	%	50.8%	49.2%	100.0%

The study population was then divided into six groups based on the platelet counts (Table 4). Bleeding manifestations were assessed in these six groups of patients. It was found that the P value is <0.001, indicating that there is significant association between platelet counts and bleeding manifestations.

The six groups of APTT values and platelet counts were compared. It was found that the Spearman rank correlation coefficient of -0.343 is present between these two variables, with a P value of <0.001.

This suggests that the finding is statistically significant. That means, as the platelet count drops, APTT value raises.

Table 4: Bleeding manifestation vs. lowest platelet count.

Bleeding	Low platelet counts												Total
	0-25000		25001-50000		50001-75000		75001-100000		100001-125000		125001-150000		
Yes	60	83.3%	11	15.3%	0	0%	1	1.4%	0	0%	0	0%	72
No	68	35.4%	70	36.5%	29	15.1%	17	8.9%	5	2.6%	3	1.6%	192
Total	128	48.5%	81	30.7%	29	11.0%	18	6.8%	5	1.9%	3	1.1%	264

DISCUSSION

Bleeding manifestations are an important clinical feature in DF. Mostly it is due to the low platelet count seen in these patients. But a significant proportion of bleeding manifestations are due to the presence of coagulopathy associated with DF. Some studies showed a high prevalence of coagulopathy of 50%,[2] but our study showed only a prevalence of only 22.3%. Coagulopathy as indicated by APTT prolongation shows abnormality in the intrinsic pathway of coagulation which lasts only for few days during the disease course. No abnormality of extrinsic pathway was found as indicated by normal PT in our study and in other earlier studies.[2] Certain studies had shown the role of IL-6 in down regulating the synthesis of factor XII, the first factor to initiate the intrinsic pathway of coagulation. APTT prolongation in the DF patients is caused by a lack of intrinsic pathway probably due to impaired synthesis of coagulation factor.[3] There are also studies showing role of activation of fibrinolytic system responsible for bleeding manifestations in dengue fever in addition to the thrombocytopenia and APTT prolongation.[3] But this was not assessed in our study because of lack of infrastructure facilities and also the high cost of investigations. This mechanism maybe responsible for the persistent elevation of APTT values in some patients even after doing mixing studies with normal plasma as evidenced by elevated D-dimer results in our study.

CONCLUSION

Dengue fever is associated with transient coagulopathy during the course of the illness. According to our study the prevalence of coagulopathy in Dengue fever is 22.3%.

In addition to the thrombocytopenia, the coagulopathy is also contributing to the bleeding manifestations seen in Dengue fever patients. Our study showed a significant correlation between bleeding manifestations with abnormal APTT values. Also the risk significantly increased with increasing values of APTT. Our study also showed a significant correlation between thrombocytopenia and abnormal APTT values which was not demonstrated in previous studies. We found that as platelet count decreases there is tendency for rise in APTT values.

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