Original Research Article

To study the clinical profile of dengue fever and to evolve a prognostic marker based on hematological parameters for severe dengue

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ABSTRACT

Background: Dengue fever is endemic to most parts of India and the clinical recognition of progression to severe dengue may become difficult in the absence of classical findings. Early recognition of shock or hemorrhage and appropriate management with fluids prevents morbidity/mortality to a great extent. In this study, we attempted to evolve a simple hematological prognostic marker for prediction of severe dengue.

Methods: This retrospective descriptive study of 67 children was conducted in the Paediatric Department of a Government Medical College. The case records of all the patients with a diagnosis of dengue fever and Severe Dengue were analysed using a preset proforma. Besides the demographic and clinical findings a detailed analysis and comparison of hematological profile was done between cases of dengue fever and severe dengue. The data obtained was analysed statistically in order to arrive at a hematological marker to predict severe dengue.

Results: Study population consisted of 67 children with 44 children with dengue fever,12 with DSS and 11 cases with DHF. Detailed analysis of hematological profile of severe dengue showed striking neutrophilia and monocytosis besides thrombocytopenia. Neutrophilia was seen in 78% and monocytosis was prevalent in 91% of cases of severe dengue. Monocytosis with thrombocytopenia was consistently seen during shock/hemorrhage. During recovery the fall of monocytes was accompanied by simultaneous increase in platelets in this group. This inverse relation was found to be statistically significant (p <0.05) Such a significant inverse correlation was not seen in dengue fever group (p >0.05).

Conclusions: Monocytosis and neutophilia are consistent features of dengue fever. There is an inverse correlation of monocytosis with thrombocytopenia in severe dengue during shock/hemorrhage which recovers on clinical improvement. Thus monocytosis with thrombocytopenia can be used as a prognostic marker to predict severe dengue.

Keywords: Dengue fever, Monocytosis , Severe dengue, Thrombocytopenia

INTRODUCTION

There is a global resurgence of dengue fever as a result of population explosion, unplanned urbanization as well as due to the lack of effective mosquito control measures.[1]

Early diagnosis and volume replacement of lost plasma with crystalloid solution can reduce the severity of dengue fever and prevent shock. At times, in the absence of hall mark clinical symptoms and signs diagnosis of impending shock/hemorrhage may be difficult.

Early prediction of this complication is crucial for timely management and favourable outcome. This study is intended to find some simple hematological guide to predict severe dengue namely dengue shock syndrome

and dengue hemorrhagic fever among cases of dengue fever.

The objective of this study was to study the clinical profile of dengue fever and to evolve a prognostic marker based on hematological parameters for prediction of severe dengue.

METHODS

This retrospective descriptive study was conducted in the Paediatrics department of a Government Medical College of South India. Data retrieval was done by perusal of case records of patients discharged with the diagnosis of dengue fever and severe dengue as per standard case definition, from January 2014 to March 2015.

The clinical profile and investigations were analyzed after data entry using a preset proforma. Hematological profile of the study population was analyzed in detail to identify prognostic indicators to predict severe dengue. Detailed statistical analysis was done using SSPS software.

RESULTS

On analysis of 67 cases, most children were in the age group of 6-10 years (45%) with an almost equal sex distribution. The most common symptoms apart from fever (98.5%) were vomiting (54%) and abdominal pain (37%). Signs most commonly noted were hepatomegaly (63%), erythematous palms/ soles (31%) and a flushed face (27%). Glossitis, throat congestion and rash were found in very few cases.

Table 1: Hematological parameters.

Hematological abnormality	Severe dengue (n = 23)		Dengue fever (n = 44)	
	No. of cases	%	No. of cases	%
Leucopenia	5	22%	18	41%
Neutrophilia	18	78%	26	59%
Monocytosis	21	91%	33	75%
Thrombocytopenia	23	100%	29	66%

Table 2. Paired sample t test -DSS group.

Parameters	Paired differences			95% CI of the difference				
	Mean	Std. deviation	Std. error mean	Lower	Upper	T test value	df	p value
Monocytes = During DSS- After recovery	4.59091	5.34125	1.61045	1.00261	8.17921	2.851	10	0.017*
Platelets = During DSS- After recovery	-0.86818	0.68101	0.20533	-1.32569	-0.41067	-4.228	10	0.002**

*significant at p < 0.05, ** very significant at p< 0.01 Table 1. Paired sample t test

Table 3: Paired sample t test -DHF group.

Parameters	Paired differences			95% CI of the difference				
	Mean	Std. deviation	Std. error mean	Lower	Upper	t test value	df	p value
Monocytes = During DHF - After recovery	4.92	5.07	1.46	1.71	8.14	3.37	11	0.006**
Platelets = During DHF- After recovery	-0.79	0.54	0.16	-1.13	-0.44	-5.06	11	0.0001***

*significant at p < 0.05, ** very significant at p< 0.01, *** Highly significant at p<0.0001

Table 4: Paired sample t test -dengue fever group.

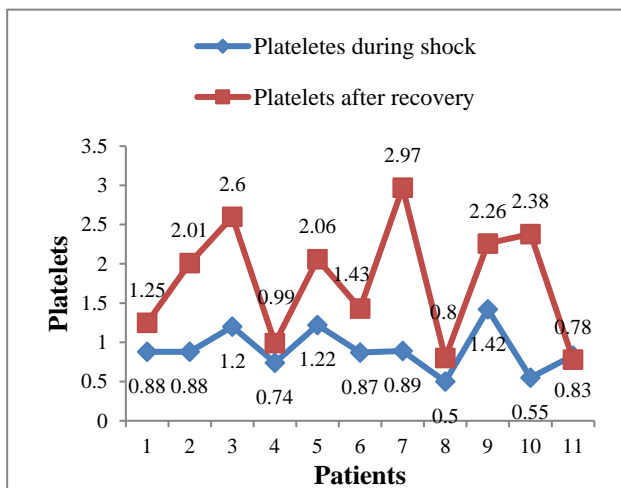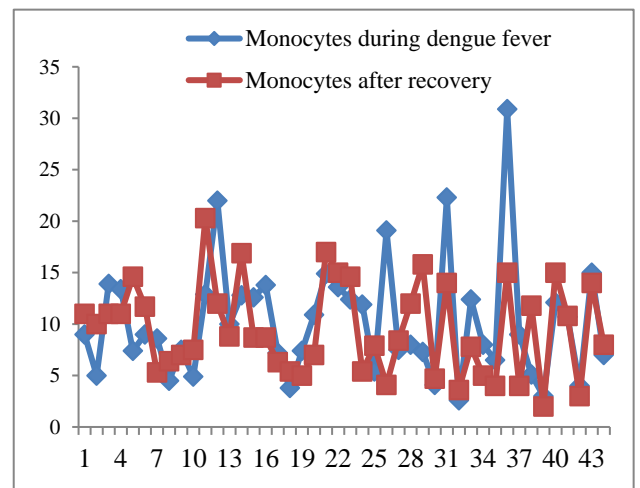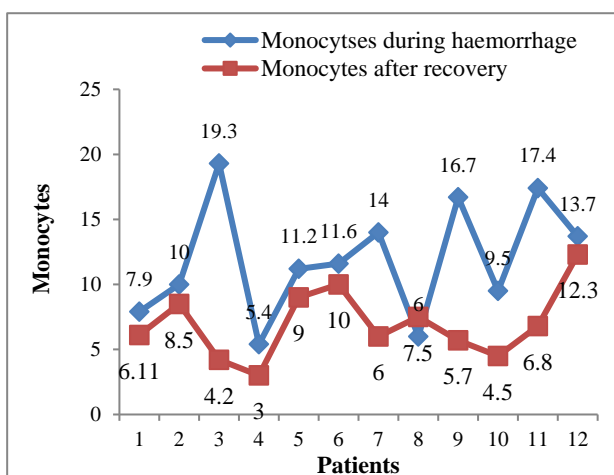| Parameters	Paired differences			95% CI of the difference				
	Mean	Std. deviation	Std. error mean	Lower	Upper	t- test value	df	p value
Monocytes during dengue fever and after recovery	0.73	5.18	0.78	-0.85	2.30	0.93	43	0.359 (NS)
Platelets during dengue fever and after recovery	0.29	1.12	0.17	-0.05	0.63	1.71	43	0.095 (NS)
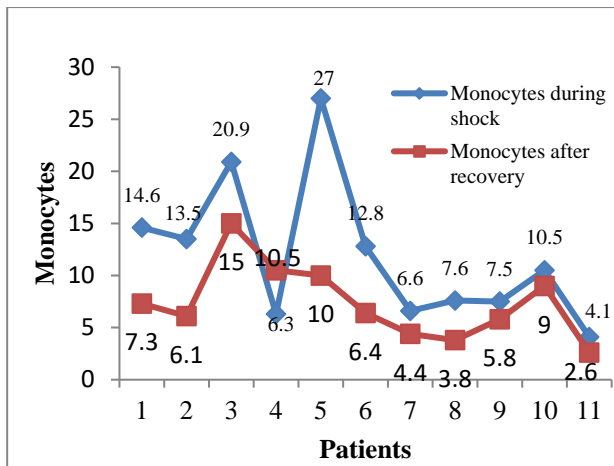
Figure 1: Monocytes during shock and after recovery (n=11).

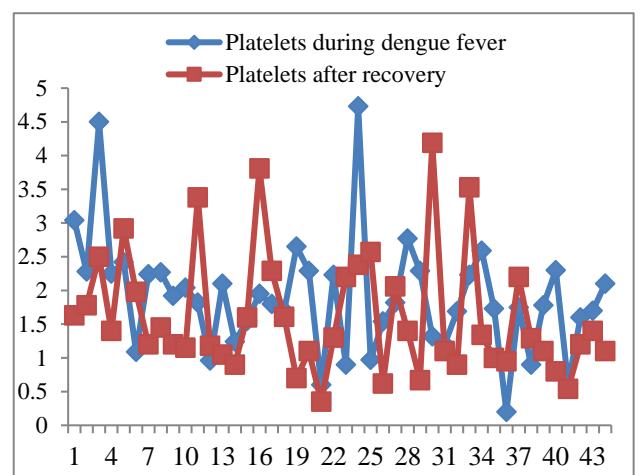**Figure 2: Platelets during shock and after recovery (n=11).**

Figure 3: Monocytes during haemorrhage and after recovery (n = 12).

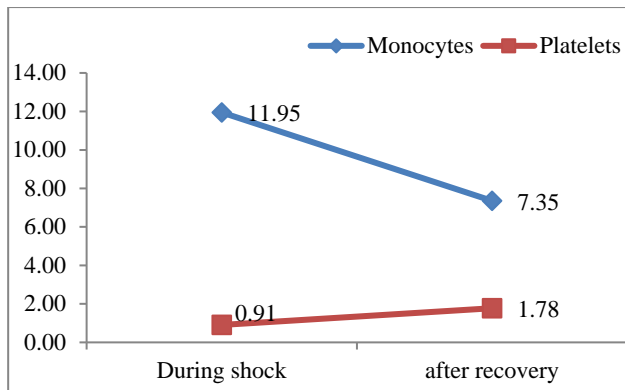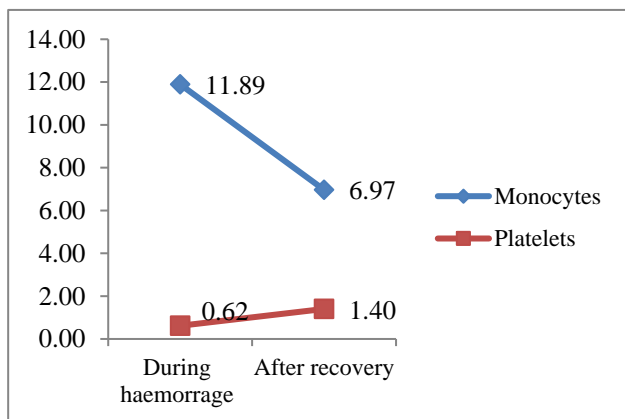**Figure 4: Platelets during haemorrhage and after recovery (n=12).**

Figure 5: Monocytes during dengue and after recovery (n=44).
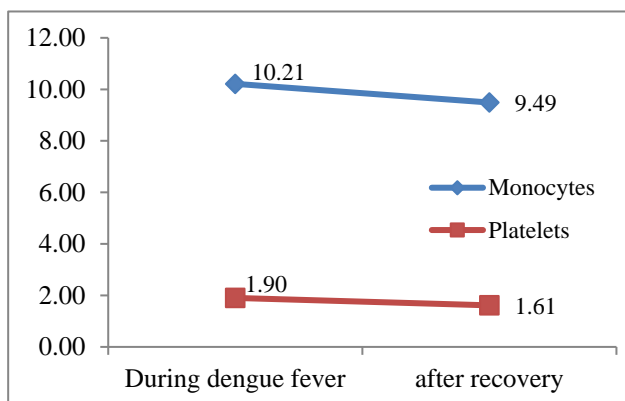

Figure 6: Platelets during dengue and after recovery (n = 44).

Figure 7: Mean difference during shock and recovery.

Figure 8: Mean difference during haemorrage and recovery.

Figure 9: Mean difference during dengue fever and recovery (uncomplicated).

Analysis of hematological parameters of the study group was done. Of the 67 cases analyzed, 34.3% (23 cases) had developed severe dengue. Among these 23 cases,11 cases had dengue shock syndrome (DSS) and 12 had dengue hemorrhagic fever (DHF). In the severe dengue (DSS/DHF) group, thrombocytopenia was observed in all the cases, neutrophilia was seen in 78% and monocytosis was prevalent in 91% of cases (Table 1). Among DSS patients it was observed that during shock there was significant monocytosis associated with thrombocytopenia. After recovery in the same patients, the monocytes decreased with a corresponding increase in platelet count Figure 1, 2. Similar inverse correlation was also noticed during the analysis of 12 DHF patients during haemorrhage and after recovery (Figure 3, 4). This association and inverse correlation was found to be statistically significant by the paired sample test in both DHF and DSS groups (Table 2 and 3). Study of the same parameters in the 44 cases of dengue fever (without severe dengue) showed no such inverse correlation between monocytes and platelets during fever and after recovery (Figure 5, 6). Paired sample test too showed that the association was not statistically significant (Table 4).

The mean monocytosis in DSS decreased from 11.95 during shock to 7.35 during recovery. The mean simultaneous platelet count increased from 0.91 lakhs/mm3 to 1.78 lakhs/mm^3 while in DHF group, the mean monocyte count decreased from 11.89 to 6.97 and simultaneous platelets increased from 0.62 to 1.4 lakhs/mm^3 (Figure 7, 8). Such a sharp fall of monocytes and increase of platelets was not evident in the dengue fever group. The mean monocyte count showed only a marginal decrease from 10.21 to 9.49 and in fact the mean platelet count decreased from 1.90 to 1.61 (Figure 9).

DISCUSSION

Dengue fever has now become almost endemic to India unlike the epidemic nature noticed earlier, which is amply borne by our study where in cases of dengue fever were recorded throughout the year with a slight increase witnessed following the rainy season.[2]

In our study, we found the maximum incidence of dengue illness in the 6 - 10 years age group as in other studies.[3] There was no significant gender preponderance. About 16.5% of our cases had no fever at admission thus emphasizing the fact that in dengue fever, monitoring for shock should continue beyond the defervescence of fever.

Gastrointestinal and respiratory symptoms like vomiting, diarrhea, abdominal pain and cough were the predominant presenting manifestations in our study. This is in contrast to other studies where headache, retro orbital pain, myalgia and arthralgia were reported as typical features, giving a clue to the diagnosis. Similarly, erythematous palms/ soles and conjunctival suffusion which are reported as hall mark signs in other studies were found in less than 1/3rd of our cases.[4]

Analysis of hematological parameters of the study group, revealed some interesting data. Monocytosis was found to be an early and consistent guide in the diagnosis of dengue fever, even in the absence of thrombocytopenia. Cross reactive antibodies, formed from previous infections, bind to the virions and enhance the entry of virions into monocytes, thus increasing their number.[5] In complicated dengue, studies from Venezuela have

reported monocytosis in 68.8% of their cases.[6] We found 75% cases with monocytosis in the dengue fever group, with 91% among severe dengue.

Thrombocytopenia which was found in all the cases of severe Dengue is explained by aberrant immune over activation following dengue virus infection. This immune activation is unable to clear the virus but leads to production of cytokines in large amounts that affect monocytes, endothelial cells and hepatocytes. Auto antibodies to platelets and endothelial cell are produced as a result of the existence of molecular mimicry between platelets/endothelial cells and dengue NS1antigen thus causing thrombocytopenia and leaky vascular endothelium.[7]

Analysis of severe dengue in our study also revealed a high degree of neutrophilia (78%) rather than lymphocytosis, ostensibly due to stress induced shift to left. Studies from Thailand have indicated that neutrophil count could be used as an acute dengue illness indicator. Authors have reported neutrophil nadir occuring by 4-5th day of fever and an elevated neutophil band count in 45.9% of their dengue haemorrhagic fevers.[8] In our study too, neutrophilia was a feature only during the first week of illness, thus justifying the hypothesis of a stress induced response.

The highlight of our study was the observation of an inverse correlation between monocytes and platelet count in severe Dengue. In the 11 cases of DSS and 12 cases of DHF, it was noted that at the time of presentation of shock or haemorrhage, monocytes were high with a low platelet count. During recovery in these cases it was again observed that the monocytes reduced with a corresponding increase in the platelet count. This association and inverse correlation was found to be statistically significant (p <0.05). Since such an association of monocyte and platelet count during the acute phase and after recovery is not seen in cases of dengue fever without complication, this association can be taken as a marker to predict severe dengue. Since it is an easily available hematological marker, presence of monocytosis with thrombocytopenia can alert the clinician regarding possible evolution to severe dengue thus helping him to decide on more close monitoring of such cases. Monocytes are the major targets of dengue virus but the virus infected monocytes subsequently undergo apoptosis to prevent the spread of virions.[8] Thus we propose that in DSS and DHF, during the height of viremia, virus infected monocytes increase, thereby causing overproduction of cytokines and auto antibodies to platelets causing thrombocytopenia. Improvement of the clinical condition occurs when the infected monocytes diminish by undergoing apoptosis, thus decreasing the viremia and improving the platelet count.

From the observations in our study we would like to propose that hematological parameters of monocytosis with thromboctopenia can be used as a marker for subsequent development of severe dengue. So serial monitoring of these parameters could warn us of the ensuing shock/haemorrhage so that close clinical monitoring and treatment with fluids can be done early to prevent morbidity. Since this simple hematological investigation is available in every hospital this marker will be useful even in resource poor settings especially during epidemics.

CONCLUSION

Neutrophilia in the first week of fever should not distract the clinician from a diagnosis of dengue fever. Presence of significant monocytosis can be used as a diagnostic guide, in the absence of thrombocytopenia, in a clinical setting of dengue fever. Inverse correlation between monocytosis and platelets can be used as a prognostic marker for prediction of severe dengue.

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