To Assess the Relative Incidence of and to Compare the Hemocytological Changes in Malaria, Dengue and Typhoid Fever or Their Combination, in Children Admitted in A Tertiary Care Centre in Western UP, India

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ABSTRACT

Introduction: There is a high incidence of acute febrile illnesses such as dengue fever, malaria and typhoid in Western UP, especially during the post rainy season months.. This study aims to assess the relative incidence and to compare the hemocytological parameters associated with these conditions.
Materials and Methods: This was the cross-sectional, prospective observational study conducted among paediatric patients admitted to a tertiary care centre in northern India. 90 patients admitted with fever of less than 3 weeks and diagnosed with dengue, malaria, typhoid or their combination were included. NS1 antigen or IgM antibodies tests were used to diagnose dengue, Card test for malaria antigen or malarial parasites on a peripheral smear to diagnose malaria and Typhidot/ Widal test to diagnose typhoid. ANOVA and logistic regression analyses were conducted to analyze the hemocytological parameters.
Results: Moderate/severe thrombocytopenia was observed with greater frequency among dengue and malaria patients with a greater severity in the latter or when both coexisted. Dengue was more often associated with high haemoglobin and low total leukocyte counts while typhoid was associated with a wide variation in the total leukocyte counts with relatively lower incidence of thrombocytopenia. Predicted probabilities suggested the likelihood of a particular disease given the hemocytological parameters in relation to the patient's age.
Conclusion: Incidence of dengue was highest followed by typhoid and malaria. Certain trends in hemocytological parameters emerged that could guide physicians on the most likely disease in the absence of formal confirmatory tests not always available at the primary care setting.

Keywords: NS1 antigen, Card test for malaria, Widal test, Thrombocytopenia, Neutrophil, Lymphocyte

INTRODUCTION

Acute undifferentiated fever (AUF) is a temporary febrile illness accompanied by non-specific symptoms. Malaria, dengue, leptospirosis and rickettsial illnesses were frequently identified as the etiologies of AUF.[1] Dengue and malaria are two major public health concerns in tropical settings. Although the pathogeneses of these two arthropod-borne diseases differ, their clinical and biological presentations may be similar. During dengue epidemics, several hundred patients with fever and diffuse pain are admitted weekly at the emergency room. It is difficult to discriminate them from patients presenting with malaria attacks.[2] Thrombocytopenia is a common finding in dengue, specially in Dengue Hemorrhagic Fever(DHF).[3] Plasmodium falciparum and Plasmodium vivax malaria are endemic infections in India and are associated with hematological abnormalities. Severe thrombocytopenia is common in isolated falciparum and mixed falciparum/vivax malaria,[4] Concurrent infection with two infectious agents, can result in an illness having overlapping symptoms, resulting in a situation where both diagnosis and treatment of a patient may become difficult for a physician.[5] Dengue infection depends on the seasonal variation of climate. The rainfall provides places for mosquitoes to lay eggs and develop to the adult stage. Temperature plays an important role in the life cycle and behaviour of mosquitoes. A very high or low temperature reduces the risk of dengue infection.[6]

Hospital-based studies and outbreak reports from India indicate that enteric fever is a major public health problem in this country, with *Salmonella enterica* serovar Typhi (*S.* Typhi) the most common aetiologic agent but with an apparently increasing number of cases due to *S.* Paratyphi A (SPA). because of risk factors such as poor sanitation, lack of a safe drinking water supply and low socio economic conditions in resource-poor countries[7] - these conditions being amplified in the post rainy season months.

There is a sudden surge in the incidence of acute febrile illness in the post-rainy season months of September to November in Western UP. A large majority of these cases are diagnosed as having dengue, malaria or typhoid fever.

The primary objective of this study was to assess the relative incidence of Dengue, Malaria and Typhoid fever or their combination in children admitted with acute febrile illness. The secondary objective was to compare the hemocytological changes in them and to assess whether they could be used to predict a particular disease,specially in the initial stages of the illness, as a substitute to the more expensive tests like NSI antigen,Typhidot or Card test for malaria which are not routinely available at the primary care setting

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MATERIAL AND METHOD

This was a hospital-based, prospective, observational study conducted between 1st September 2015 and 15th November 2015 at a tertiary care hospital in western Uttar Pradesh, India. A total of 90 patients who were *admitted* with fever of short duration (3 to 15 days) and diagnosed as having either dengue, typhoid or malaria, or a combination of these were included in this study. Patients diagnosed with other causes of fever and those suffering from acute febrile illness and receiving outpatient treatment were excluded from the study. Specific tests to confirm dengue(NS1 Antigen and IgM antibodies), typhoid fever (Widal test/Typhidot) and malaria (a Peripheral Blood Smear or a card test for malaria antigen (vivax or falciparum) were done.Only patients with a confirmed diagnosis based on relevant investigations were included in the present study. Complete hemogram which included a hemoglobin percent, a total and differential leukocyte count and platelet count were done at the time of presentation to the hospital and these records were analyzed in the present study.

Patients were classified by disease status and severity of thrombocytopenia (disease-thrombocytopenia category, hereafter). Those with a positive NS1 antigen *or* IgM antibodies test were classified as having dengue, positive Widal/ Typhidot as typhoid and positive Malaria Antigen/ IgM/GBP tests as malaria. Positive test results on two or more tests suggested a combination of these diseases. Thrombocytopenia was defined as platelet count below 150,000 with severity depending on the extent of fall in platelet count: platelet count between 100,000 and 150,000 was defined as mild, between 50,000 and 100,000 as moderate and below 50,000 as severe thrombocytopenia.[8]

STATISTICAL ANALYSIS

Five hemocytological parameters were analyzed- platelet count, haemoglobin (Hb), total leukocyte count (TLC), neutrophils and lymphocytes. Mean values) of these parameters in each disease-thrombocytopenia category were calculated. Differences in these mean values across disease categories were tested using analysis of variance (ANOVA) / Student's t-test (for normally distributed variables) and Kruskal-Wallis test/ Mann-Whitney-Wilcoxon test (for non-normal variables), as appropriate. Ordered logistic regression was conducted to determine the relationship between thrombocytopenia and blood cell counts. Logistic regression analyseswere conducted to estimate the predicted probabilities for a particular disease. Differences were considered statistically significant at the 5% significance level. All analysis was conducted using Stata 13.

RESULTS

Of the 90 patients under study, 61(67.78 %) had dengue, 24(26.67%) had malaria and 31(34.44 %) had typhoid, with or without overlap (Table 1). 41(45.6%) patients had only dengue, 13(14.4%) had only malaria and 12(13.3%) had only typhoid. 5(5.6%) patients had both dengue and malaria, 13(14.4%) patients had both dengue and typhoid, 4(4.4%) had typhoid and malaria whereas 2(2.2%) had all three illnesses viz. dengue, typhoid and malaria.

Demographic characteristics of the patients, both in the total sample and by disease status, are reported in Table1.Ages ranged from 6months to 15 years with a mean age of 9.8 years. Over half of the patients (58.88%) patients were aged 10-15 years, 30% were aged 5 to <10 yrs and 11.1 % were < 5 years old. Patients having dengue (alone or with other diseases) were relatively older (mean age of such patients was 11.07years, only one of them being an infant).. Mean age of patients with malaria (alone or in combination) was 7.40years while those with typhoid (alone or in combination) was 9.77years. There was no sex predilection in the sample with 46 patients being female and 44 male. This was also largely true within each disease category, although both patients with all three diseases were females. Age distribution *within* male and female samples was also similar.

Over half of all patients (62.2%) in the sample had moderate or severe thrombocytopenia (Table 2). Thrombocytopenia was observed in majority of patients having only dengue (80.48%) and only malaria (92.3 %), with most of these being in the moderate/severe range (71% for dengue only and 61.5% for malaria only). However only 33.3 % having only typhoid had thrombocytopenia. All patients having both dengue and malaria had moderate/severe thrombocytopenia. 76.92% of patients having both dengue and typhoid and 75% patients having both typhoid and malaria had thrombocytopenia. Interestingly, both patients having all three illnesses had only moderate thrombocytopenia.

Mean platelet count among patients in each disease-thrombocytopenia category are shown in Table 3. Overall, mean platelet count was lowest among patients with both malaria and dengue (49,800/mm^3) and highest among those with typhoid only (1,81,250/mm^3). However, there was no statistically significant difference in mean platelet count levels across disease categories (P=0.108). Comparing each of the other disease categories to the dengue only group, only

	No. of patients (%)	Age (years), Mean(SD)	Male, No. (%)	Female, No. (%)
Total sample	90 (100)	9.85 (3.88)	44 (48.9)	46(51.1)
Disease				
Dengue Only	41 (45.6)	10.96 (3.48)	22 (53.66)	19 (46.34)
Malaria + Dengue	5 (5.6)	9.6 (1.34)	2 (40)	3 (60)
Malaria Only	13 (14.4)	6.6 (4.44)	8 (61.54)	5 (38.46)
Typhoid + Dengue	13 (14.4)	12.23 (1.74)	4 (30.77)	9 (69.23)
Typhoid + Malaria	4 (4.4)	6.13 (3.71)	2 (50)	2 (50)
Typhoid Only	12 (13.3)	8.37 (4.14)	6 (50)	6 (50)
Dengue + Malaria + Typhoid	2 (2.2)	9.5 (2.12)	0 (0)	2 (100)

Table-1: Characteristics of patient population

patients with typhoid only had a significantly higher mean platelet count (P=0.013) while the difference was not statistically significant for all other groups when compared with Dengue only.

Haemoglobin ranged from 3.8g% to 15g%, with mean hemoglobin being highest in cases of"dengue only" (10.4g%) followed by "typhoid plus dengue" (10.3g%) and "typhoid only" groups (8.9g%) (Table 4). It was lowest among patients with "typhoid and malaria" (6.5g %). This difference in mean haemoglobin across disease categories was statisti-

	Thrombocytopenia				
Disease	**Absent**	**Mild**	**Moderate**	**Severe**	**Total**
Dengue Only	8	4	15	14	41
	(38.1)	(30.8)	(50)	(53.8)	(45.6)
Malaria + Dengue	0	0	2	3	5
	(0)	(0)	(6.7)	(11.5)	(5.6)
Malaria Only	1	4	5	3	13
	(4.8)	(30.8)	(16.7)	(11.5)	(14.4)
Typhoid + Dengue	3	3	4	3	13
	(14.3)	(23.1)	(13.3)	(11.5)	(14.4)
Typhoid + Malaria	1	2	0	1	4
	(4.8)	(15.4)	(0)	(3.8)	(4.4)
Typhoid Only	8	0	2	2	12
	(38.1)	(0)	(6.7)	(7.7)	(13.3)
Dengue+ Malaria + Typhoid	0	0	2	0	2
	(0)	(0)	(6.7)	(0)	(2.2)
Total Sample	21	13	30	26	90
(Percentages in parentheses)					

Table-2: Distribution of patients according to severity of thrombocytopenia and disease

	Thrombocytopenia				
Disease	**Mean platelet count in patients with no thrombocytopenia**	**Mean platelet count in patients with mild thrombocytopenia**	**Mean platelet count in patients with moderate thrombocytopenia**	**Mean platelet count in patients with severe thrombocytopenia**	**Overall mean platelet count**
Dengue Only	2,07,500.00	1,17,500.00	63,933.30	29,771.40	85,507.30
Malaria + Dengue			80,000.00	29,666.70	49,800.00
Malaria Only	1,50,000.00	1,12,500.00	71,600.00	28,666.70	80,307.70
Typhoid + Dengue	1,66,666.70	1,13,333.30	66,250.00	39,000.00	94,000.00
Typhoid + Malaria	2,20,000.00	1,20,000.00		20,000.00	1,20,000.00
Typhoid Only	2,50,500.00		65,000.00	20,500.00	1,81,250.00
Dengue + Malaria + Typhoid			75,000.00		75,000.00
Total Sample	2,15,904.80	1,15,384.60	67,400.00	29,607.70	98,064.40

Table-3: Pattern of thrombocytopenia (as represented by mean platelet count) in relation to the causative disease

	Mean Hemoglobin in various diseases and its association with degree of Thrombocytopenia				
Disease	**Mean hemoglobin in patients with no thrombocytopenia**	**Mean hemoglobin in patients with mild thrombocytopenia**	**Mean hemoglobin in patients with moderate thrombocytopenia**	**Mean hemoglobin in patients with severe thrombocytopenia**	**Overall mean hemoglobin**
Dengue Only	9.9	11	9.6	11.3	10.4
Malaria + Dengue			8.7	7.2	7.8
Malaria Only	7	9.1	6.4	7.5	7.4
Typhoid + Dengue	8.5	11.5	9.9	11.2	10.3
Typhoid + Malaria	5.5	8.3		3.8	6.5
Typhoid Only	9		11.8	5.8	8.9
Dengue + Malaria + Typhoid			6.6		6.6
Total Sample	9	10.2	9	9.6	9.3

Table-4: Pattern of anemia (as represented by mean Hemoglobin %) in relation to the causative disease and its association with degree of Thrombocytopenia

cally significant both overall (P<0.001) and among moderate and severe thrombocytopenia cases (P=0.029 and P=0.001, respectively). This difference was, however, not significant for patients with mild or no thrombocytopenia.

There was no significant correlation between mean haemoglobin levels and severity of thrombocytopenia across any of the disease categories, controlling for age and gender. In cases of" malaria only", it was lowest in moderate thrombocytopenia (6.4g %) and maximum in mild thrombocytopenia(9.1g%) cases. Although, there was some correlation among cases of malaria with dengue, this was not statistically significant.

Differences in mean Total Leucocyte Count (TLC) were statistically significant across disease categories(P=0.018). It was lowest in cases of "malaria with dengue" (3,940/mm^3), and maximum in cases of" typhoid only" (8,933/mm3). Relative to "dengue only", mean TLC was significantly higher among cases with" typhoid only" and those with all three diseases (4150/mm^3 vs. 8933/mm^3, P=0.003 and 4150/mm^3 vs. 7000/mm^3, P=0.035, respectively).

Overall, in the total sample there was a significant direct relationship between leucopenia and severity of thrombocytopenia (P=0.007).

Results for neutrophil and lymphocyte counts were similar (Table 6 and Table 7). Both measures varied significantly across disease categories (P=0.020 for neutrophil count and P=0.021 for lymphocyte count). No significant correlation was observed between severity of thrombocytopenia and neutrophil and lymphocyte counts, respectively. Although neutrophil counts reduced while lymphocyte counts increased in the typhoid only group as severity of thrombocytopenia increased (71.6% (Neutrophils) and 25.8% (lymphocytes) for no thrombocytpenia vs. 46% (neutrophils) and 49.5% (lymphocytes) for severe thrombocytopenia), this was not significant (P=0.096 (neutrophils); P=0.069 (lymphocytes)).Mean percentage of neutrophils was higher in patients having "typhoid only"(67%) and least in patients with" malaria with Dengue"(50.6%).

There was no clearly identifiable hemocytological pattern pathognomonic of any of these diseases However predicted probabilities derived from logistic regression analyses suggest some trends in hemocytological changes associated with each disease viz:

1. There is a higher probability of Dengue fever in the age group 10.96 $\pm$ 3.48 years:
   a. If TLC is <4000/cumm, Platelet count 50000-100000/cumm,neutrophil count between 40- 80% and lymphocyte count is 20-40% or
   b. If TLC is <4000/cumm, Platelet count 100000-150000/cumm and neutrophil count >80% or

	Mean TLC in various diseases and its association with degree of Thrombocytopenia				
Disease	**Mean TLC in patients with no thrombocytopenia**	**Mean TLC in patients with mild thrombocytopenia**	**Mean TLC in patients with moderate thrombocytopenia**	**Mean TLC in patients with severe thrombocytopenia**	**Overall mean TLC**
Dengue Only	5,785.70	2,950.00	4,321.40	3,453.80	4,150.00
Malaria + Dengue			3,550.00	4,200.00	3,940.00
Malaria Only	4,100.00	4,133.30	5,850.00	5,933.30	5,245.50
Typhoid + Dengue	4,366.70	4,033.30	5,200.00	3,933.30	4,446.20
Typhoid + Malaria	11,800.00	6,700.00		2,000.00	6,800.00
Typhoid Only	11,175.00		5,650.00	3,250.00	8,933.30
Dengue + Malaria + Typhoid			7,000.00		7,000.00
Total Sample	7,945.00	4,141.70	4,896.40	3,824.00	5,191.80

Table-5: Pattern of leucopenia (as represented by mean total leucoyte count) in relation to the causative disease and its association with degree of Thrombocytopenia

	Mean Neutrophil count in various diseases and its association with degree of Thrombocytopenia				
Disease	**Mean Neutrophil count in patients with no thrombocytopenia**	**Mean Neutrophil count in patients with mild thrombocytopenia**	**Mean Neutrophil count in patients with moderate thrombocytopenia**	**Mean Neutrophil count in patients with severe thrombocytopenia**	**Overall mean Neutrophil count**
Dengue Only	68.7	67.3	59.3	63.5	63.4
Malaria + Dengue			55.5	47.3	50.6
Malaria Only	45	53.7	50	52.3	51.3
Typhoid + Dengue	68.7	60.7	64	71	65.9
Typhoid + Malaria	64	47		65	55.8
Typhoid Only	71.6		69.5	46	67
Dengue + Malaria + Typhoid			72		72
Total Sample	68.5	58.8	60.4	59.8	61.9

Table-6: Mean Neutrophil count in relation to the causative diseases and its association with degree of Thrombocytopenia

	Mean Lymphocyte count in various diseases and its association with degree of Thrombocytopenia				
Disease	**Mean Lymphocte count in patients with no thrombocytopenia**	**Mean Lymphocte count in patients with mild thrombocytopenia**	**Mean Lymphocte count in patients with moderate thrombocytopenia**	**Mean Lymphocte count in patients with severe thrombocytopenia**	**Overall mean Lymphocyte count**
Dengue Only	27.4	31	37.2	33.9	33.5
Malaria +Dengue			40.5	47.3	44.6
Malaria Only	52	42	48	43.3	45.2
Typhoid + Dengue	24.3	37.7	31.3	26	29.9
Typhoid + Malaria	34	48		30	40
Typhoid Only	25.8		28	49.5	30.1
Dengue + Malaria + Typhoid			24		24
Total	27.9	38.3	36.1	36.8	34.6

Table-7: Mean Lymphocyte count in various diseases and its association with degree of Thrombocytopenia

   c. If TLC is <4000/cumm, Platelet count <50000/cumm and lymphocyte count is 20-40%
2. There is a higher probability of Malaria in the age group 6.6 ±4.44 years:
   a. If TLC is 4000-8000/cumm, Platelet count is 100000-150000/cumm and neutrophil count is 60-80% or
   b. If TLC is 4000-8000/cumm, Platelet count is 50000-100000/cumm and neutrophil count is 20-40%
3. There is a higher probability of Typhoid Fever in the age group 8.37 ±4.14 years:
   a. If TLC is <4000/cumm or >12000/cumm, lymphocyte count is <20% and Platelet count is normal or
   b. If TLC is 8000-12000/cumm, neutrophil count is 20-40% and Platelet count is normal

DISCUSSION

This study was performed at a tertiary care centre of Western UP between the months of September to mid November -this being the peak season for Dengue fever, Malaria and typhoid or a combination of these[9]

In the present study 61(67.78%) patients were diagnosed as having dengue fever on the basis of their blood being positive for NS1 antigen [18/61 (29.5%)] or IgM antibodies [47/61 (77.05%)] or both. Tan R Kurniawan et al also observed that when suspected dengue samples were tested by all methods, viral isolation detected the fewest dengue infections (10.5%), while the IgM/IgG ELISA was the most successful (46.3%) in diagnosing dengue infections.[10] In 18 cases who had positive NS1 antigen IgM was negative in 8 cases which could be due to the timing of the tests as the IgM appears 5-10 days after the infection.

Typhoid fever was diagnosed on the basis of Typhi Dot or Widal test which was found to be positive in 31 cases out of the total sample population of 90 patients(34.4%).

Malaria was diagnosed on the basis of general blood picture and/or positive card test for Malaria and was found to be positive in 24 patients out of the total of 90(26.66%)

Amongst patients with malaria, 12 were male and 12 female. Dengue was present in 28 males and 23 females included in the study while 13 males and 18 females presented with typhoid. Mean age of patients having Dengue fever alone or in combination was 11.07 years which is in accordance with Rathi et al[11] who also observed a mean of 11.6 years in their study, whereas it was 9.77 years for typhoid and 7.40years for Malaria. There was no sex predilection for any of the diseases in our study which is in contrast to Rathi et al who have reported a preponderance of male population in their study in rural Rajasthan which could be due to highly prevalent gender bias there.

Thrombocytopenia was observed in 80% cases of "dengue only", 92.3% cases of "malaria only" and just 33% cases of "typhoid only" subgroups. The mean platelet count in cases of "dengue only" was 85507.3, in malaria only was 80,307.7 and in "typhoid only" was 1,81,250). The mean hemoglobin was lowest in cases of "malaria only",(7.4g%) and highest in cases of "dengue only" (10.4g%). This can be explained by the hemolysis characteristic of malaria and the hemoconcentration that occurs in dengue because of capillary leakage.. In cases of pure typhoid fever also, Hb was less than normal. This could be because of bone marrow suppression that occurs in infections of longer duration or because of the high prevalence of iron deficiency anemia in our country, specially in the lower socioeconomic population in whom chances of GI infections also would be more. Underlying nutritional deficiency anemia could also explain the relatively low Hb levels in dengue, despite the hemoconcentration due to capillary leakage. In cases having both malaria and typhoid, hemolysis due to malaria was superimposed on diminished hematopoiesis leading to very low Hb levels (upto 2.9g% in our study).

The mean TLC was lowest in cases of "dengue only" with mild thrombocytopenia. This shows that leucocyte production is also reduced in dengue along with the platelets. However the degree of leucopenia did not correlate with the degree of thrombocytopenia in these cases. In cases of typhoid, leucocyte counts were highest in cases without thrombocytopenia and decreased serially as the thrombocytopenia increased. This could result from the increasing bone marrow suppression with increasing severity of the disease. It was observed that most severe thrombocytopenia occurred when both dengue and malaria coexisted(5 cases), with severe thrombocytopenia present in 3 cases, having a mean platelet count of 29,666.7/mm^3 and moderate thrombocytopenia

present in 2 cases with a mean platelet count of 80,000/mm^3. Logistic regression was used to identify trends in hemocytological parameters in conjunction with age groups of the patient population to predict the causative disease,which could be used at the primary care setting.

CONCLUSIONS

This study observed the highest incidence of Dengue among all causes of acute undifferentiated fever followed by Typhoid and Malaria. However the incidence of thrombocytopenia was higher in cases of Malaria as compared to Dengue against the popular notion to the contrary.

There was no clearly identifiable hemocytological pattern pathognomonic of any of these diseases. However on the basis of statistical analysis certain trends were observed indicating a higher probability of a particular disease

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