Hematological Manifestations of Dengue, Malaria and Enteric Fever in Children Presenting To a Tertiary Care Hospital, Pakistan.

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Abstract

Objective: Dengue fever, Malaria and Enteric fever are common pediatric acute febrile illnesses, presenting with overlapping clinical manifestations. The hematological parameters of these disease may give a clue to the specific diagnosis before definitive investigations are available. We designed this study to determine the hematological predictors of dengue fever, malaria and enteric fever in pediatric inpatient population.

Methods: We collected data for this observational study from May to October 2022 from Pediatrics Department, Dr. RKMP Civil Hospital Karachi. We reviewed the medical records of patients 1 month to 12 years of age admitted with definitive diagnosis of dengue, malaria and/or enteric fever. We recorded the demographic and clinical variables and hematologic parameters of Complete Blood Count and calculated the P value and sensitivity / specificity of each parameter in SPSS 22.0, for differentiating the three diseases.

Results: A total of 205 patients were included in the study, out of which 82 (40%) had malaria, 71 (34.6%) had dengue and 52 (25.4%) had enteric fever. Male gender was predominant in 73.6%. Patients with dengue fever mostly had normal hemoglobin (>11gm/dl) with a higher hematocrit, lymphopenia (<40%) and thrombocytopenia (50,000-100000/ul), while in enteric fever moderate anemia (7-9gm/dl) with normal TLC and platelet count was mostly found and for malaria severe anemia (<7gm/dl) and thrombocytopenia (<50,000/ul) with a normal TLC count were predictive of disease (P value<0.05).

Conclusion: Lymphopenia and Thrombocytopenia are predictors of dengue fever, moderate anemia with preserved platelet count suggests enteric fever while severe anemia and thrombocytopenia should predict malaria in the appropriate clinical setting.

Key words: Dengue, Malaria, Enteric fever, Anemia, Thrombocytopenia, Infectious diseases.

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Introduction

Pakistan is among those developing countries which are still trying to control infectious diseases. We still have a high under-5 mortality rate of 65 per 1000 live births as per the recent World Bank data, with infectious diseases being the leading the cause of mortality[1]. The recent heavy monsoon and flood situation this year has further worsened the condition, leading to outbreaks of various mosquito-borne and water-borne diseases including dengue, malaria and enteric fever. The initial clinical presentation of all three of these diseases are as acute febrile illness with non-specific symptoms such as nausea, vomiting, malaise, anorexia and headache which can make a clinical-presentation-based diagnosis difficult[2-4]. There are various hematological manifestations of these diseases, as manifested in the complete blood count (CBC), which can help in making an appropriate provisional diagnosis in cases with non-specific clinical features[5,6]. The hematologic manifestations of these disorders involve

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all three cell lines and can vary from anemia, bicytopenia and pancytopenia to leukocytosis and lymphocytosis[7]. These parameters picked early may also predict the clinical outcome in infected children[8].

We recently observed a high influx of patients presenting as non-specific acute febrile illness in our department, with overlapping clinical manifestations and on definitive investigations proved to be either dengue fever, malaria or enteric fever. Thus, we designed this study to differentiate these three causes of acute febrile illness on the basis of hematological findings. This study will help the clinicians in making a better provisional diagnosis by evaluating complete blood count till diagnostic laboratory results are available. Thus, timely management will be possible resulting in decreased morbidity and mortality.

Methodology

We performed a retrospective, observational study, at the Department of Pediatrics of Dr. RKMP Civil Hospital Karachi, after approval from Institutional Review Board (IRB) of Dow University of Health Sciences. As it is a retrospective study, we fixed the duration of sampling for 6 months and collected the data of all patients fulfilling the inclusion criteria during the study period. The sample was collected from May 2022 till October 2022 by convenience sampling. We reviewed the admission files of all patients admitted in the pediatric ward during the study period and patients who were 1 months to 12 years of age, of both genders, who were diagnosed with dengue fever, malaria and/or enteric fever were included in the study. The diagnosis of dengue fever was made on positivity of either NS1 antigen or Dengue IgM antibodies. Enteric fever was diagnosed on basis of positive blood culture growth of salmonella typhi while malaria was diagnosed on detection of malarial parasite on peripheral smear. Incomplete files and patients who had diagnosed chronic hematologic disorders were excluded from the study. Data was extracted by the principal and co investigators and collected on a predesigned proforma which included demographic variables like age and gender, clinical variables including diagnosis, signs, symptoms and hematological parameters as evident in the complete blood count (CBC). CBC is done as a routine investigation on the day of admission in all patients presenting with fever. Hematologic parameters assessed were hemoglobin for anemia, hematocrit, total leucocyte count (TLC) for leucopenia or leucocytosis and platelet count for thrombocytopenia or thrombocytosis.

All data was anonymized to ensure privacy of the patients. Data was entered and analyzed in SPSS version 22.0. Frequencies and percentages were calculated for categorical variables and mean & standard deviation for continuous variables. Chi square test was applied to calculate P-value for individual variables and P value of <0.05 will be taken as significant. Univariate multinomial logistic regression model was performed to confirm that associations between variables were independent of age, gender, and residence. Sensitivity and specificity were calculated for each hematological parameter for differentiating the three diseases.

Results

A total of 205 patients were included in the study, out of which 82 (40%) had malaria, 71 (34.6%) had dengue fever and 52 (25.4%) had enteric fever. Male gender and residence in urban area (Karachi) was significantly predominant in all three diseases (p-value 0.0005). Median age of the patients was 4 years, 5 years and 6 years for typhoid fever, malaria and dengue fever respectively. There were 03 patients with dengue fever coexisting with malaria, 01 patient of dengue fever with enteric fever and 01 patient of enteric fever with malaria.

Fever was the most common sign present in all 205 (100%) patients, of all three diseases, as a presenting complaint, followed by loss of appetite. Nausea and vomiting were common in dengue 32 (45.1%) and enteric fever 23 (44.2%) as compared to malaria 14 (17.1%). Flushing, bleeding, body aches, headache, retro-orbital pain and backache were significantly more common in dengue fever (p value < 0.05). Hepatomegaly, coated tongue and anemia were the common signs in enteric fever, while anemia, splenomegaly and hepatomegaly were common in malaria. Details of the clinical manifestations are given in Table 1.

Table 1. Clinical characteristics of patients with Dengue, Malaria and Enteric fever.

Variables	Dengue Fevern =71n (%)	Entericfevern =52n (%) n(%)	Malarian =82n (%) n(%)	P-Value
Symptoms				
Fever	71 (100)	52 (100)	82 (100)	
Loss of appetite	66 (93)	35 (68.6)	40 (48.8)	0.0005
Nausea	32 (45.1)	23 (44.2)	12 (14.6)	0.0005
Vomiting	32 (45.1)	23 (44.2)	14 (17.1)	0.0005
Diarrhea	13 (18.3)	14 (26.9)	4 (4.9)	0.002
Abdominal pain	36 (50.7)	25 (48.1)	24 (29.3)	0.015
Abdominal distention	14 (19.7)	2 (3.8)	6 (7.3)	0.008
Flushing	34 (47.9)	Nil	6 (7.3)	0.0005
Itching	8 (11.3)	Nil	2 (2.4)	0.007
Bleeding	27 (38)	1 (1.9)	2 (2.4)	0.0005
Generalized body ache	40 (56.3)	11 (21.2)	30 (36.6)	0.0005
Headache	9 (12.7)	Nil	8 (9.8)	0.035
Retro orbital pain	9 (12.7)	Nil	Nil	0.0005
Backache	8 (11.3)	Nil	Nil	0.0005
Signs				
Rashes	16 (22.5)	Nil	2 (2.4)	0.0005
Anemia	16 (22.5)	32 (62.7)	66 (80.5)	0.0005
Coated Tongue	10 (14.1)	31 (62)	Nil	0.0005
Hepatomegaly	26 (36.6)	36 (69.2)	44 (53.7)	0.002
Splenomegaly	9 (12.7)	8 (15.4)	60 (73.2)	0.0005
CNS finding	4 (5.6)	1 (1.9)	8 (9.8)	0.185

Majority of patients with malaria had low hemoglobin level of <7 gm/dl, while most patients of enteric fever had a hemoglobin level of 7-9 gm/dl and most patients with dengue fever had hemoglobin of > 11gm/dl (P value 0.0005). Similarly most patients of dengue had a higher hematocrit level as compared to most patients of malaria who had the lower hematocrit level (P value 0.0005). Surprisingly there was no significant difference in the leucocyte count among the three diseases (P value 0.6) as well as the neutrophil percentage (P value 0.2), but most patients of dengue had lymphocytes <40% as compared to patients with malaria who mostly had lymphocytes >40% (P value 0.0005). Most patients of enteric fever had platelet count >150,000/ul as compared to most patients of malaria having platelet count of <50,000/ul (P value 0.00005). After adjusting for age, gender, and residence in the univariate regression model, the difference of hemoglobin, lymphocyte count and platelet count between dengue fever and malaria was not confounded and the difference of platelet count between malaria and enteric fever was also not confounded i.e., they were significant (P < 0.05) (Table 2).

Table 2. Univariate analysis of dengue/malaria and typhoid / malaria infection, with Hematological parameters adjusted by age, gender and residence

Parameter	Dengue vs. Malaria OR	[95%CI]	P-value	Typhoid vs. Malaria OR	[95%CI]	P-Value
Hemoglobin (gm/dl)						
<9	0.01	0.002-0.047	0.0005	0.515	0.059-4.51	0.549
9-11	0.03	0.005-0.164	0.0005	1.52	0.155-14.94	0.718
>11			Ref			Ref
Hct (%)						
<30 or >40 **30-40**	0.11	0.045-03.26	0.0005 REf	0.69	0.26-1.84	0.460 Ref
Total leucocyte count (/ul)						
Leukocy -tosis	3.23	0.90-11.58	0.072	0.91	0.18-4.47	0.906
Leucopenia	2.61	1.08-6.32	0.033	2.01	0.73-5.65	0.177
Normal			Ref			Ref
Neutrophil (%)						
<70% (%) **e"70%**	0.34	0.11-1.12	0.077 Ref	0.48	0.13-1.78	0.276 Ref
Lymphocyte (%)						
<40%	3.78	1.79-7.97	0.0005	1.97	0.85-4.56	0.110
>40%			Ref			Ref
Platelet count (/ul)						
<50,000	29.78	3.44-258	0.002	0.057	0.01-0.24	0.0005
50,000 – 150,000	19.06	2.27-160.23	0.007	0.195	0.06-0.58	0.004
>150,000		Ref			ref	

For differentiating between dengue fever and malaria, the specificity of hematocrit >40 was 100%, sensitivity and specificity of lymphocyte count <40% was 70.4% and 65.8%, while sensitivity of platelet count <150,000 was 98.6%. For differentiating between enteric fever and malaria, sensitivity of Hb < 11 was 96.2%. Details are in Table 3.

Table 3. Sensitivity and specificity of hematological parameters for differentiating between Dengue fever vs Malaria and Enteric fever vs Malaria.

Variable	Cutoff	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
		Dengue fever	vs Malaria	Dengue fever	vs Malaria
Hemoglobin (gm/dl)	<11	32.4	2.4	96.2	2.4
Hct	<30	22	14.6	73.1	14.6
	>40	20.7	100	- -	
TLC (/ul)	>10x10^3	17.7	90.6	10.3	90.6
	<4x10^3	32.3	76.3	27.1	76.3
Neutrophil (%)	<70%	84.5	7.32	84.6	7.32
Lymphocyte (%)	<40%	70.4	65.8	51.9	65.8
Platelet count (/ul)	<150000	98.6	17.1	38.5	17.1

Discussion

Dengue fever, malaria and enteric fever are common infectious disorder which pediatricians come across in their daily practice, in patients presenting with fever. This study is an attempt to differentiate the three disorders on basis of their hematologic manifestations. Most of the patients in our sample population were male in all three disease groups. Same finding is reported by other researchers from Pakistan for all three diseases [9-11]. The age group of our patients was 4, 5 and 6 years for enteric fever, malaria and dengue fever respectively. Hussain et al[11] also reported age of presentation of dengue fever at 5.7 years, similar to ours, but Khan et al[12] reported mean age of malaria presentations to be 7 years and Ahmad et al[13] found enteric fever patients with a mean age of 6 years which are higher than ours.

Among clinical manifestations, fever followed by loss of appetite, abdominal pain, nausea and vomiting were the commonest symptoms in all three of these acute febrile illnesses in our cohort, which makes the clinical diagnosis confusing. The significant differentiating features in dengue fever were flushing, bleeding manifestations and aches including generalized bodyache, headache, retroorbital pain and backache. Similar manifestations helpful in differentiating dengue fever from other febrile illnesses were reported by Chaloem wong et al[5] and Rosenberger et al[14]. Nausea and vomiting were common in both enteric and dengue fever in our cohort. We found that the combination of abdominal pain, diarrhea and generalized body ache with coated tongue and hepatomegaly was more common in enteric fever. Aiemjoy et al[15] performed a multinational study to differentiate enteric fever from other febrile infections and found results similar to ours, that patients <15years of age diagnosed with enteric fever from Pakistan had cough, diarrhea, abdominal pain, vomiting and headache as the common complaints. In our study, patients with malaria had a clinically differentiating combination of anemia, splenomegaly and hepatomegaly. Anemia as a common presentation of malaria has been similarly reported by other authors too[16,17].

Among hematological manifestations, most patients with dengue fever had non- confound and statistically significant hemoglobin of >11 gm/dl, hematocrit of >40, TLC was within normal range, with lymphocytes < 40% and neutrophils < 70% and platelet count mostly lying in the range of 50,000 to 100,000 /ul. HCT>40 and lymphocytes <40% were sensitive and specific for differentiating dengue and malaria. Similar findings were observed by Kotepui et al[4] in Thailand and Asghar et al[18] in Rawalpindi, Pakistan. Most patients with enteric fever had hemoglobin between 7 to 9 gm/dl, normal TLC count, neutrophils <70%, lymphocytes <40% and normal platelet count. Similar findings of most patients having normal TLC count and normal platelets was found by Behera et al[19] in India and Tashfeen et al[20] from Quetta, Pakistan. In most patients with malaria, we found non- confound and statistically significant severe anemia (Hemoglobin <7) and thrombocytopenia (platelets < 50,000) while TLC was normal with lymphocytes mostly > 40%. Other researchers have also documented significant proportion of patients with thrombocytopenia in cases of malaria[12,21]. Some researchers have also found equivocal results of platelet count in patients with malaria[22]. Thus, the significant hematological predictors in our study for dengue fever were normal hemoglobin with a higher hematocrit, lymphopenia and thrombocytopenia, for enteric fever

moderate anemia with normal TLC and platelet count and for malaria severe anemia and thrombocytopenia with a normal TLC count.

This study has some limitations. It is a retrospective design and a single – center study. More prospective studies can be done on similar topic to look at the progression of these hematologic parameters during the course of disease and their effect on the morbidity of disease.

Conclusion

In patients with acute febrile illness, high hematocrit with thrombocytopenia, lymphopenia and normal hemoglobin should suggest dengue fever while moderate anemia with normal platelet count should suggest enteric fever. Severe anemia and thrombocytopenia should be highly suggestive of malaria infection.

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