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Clinical and Laboratory Evaluation of Patients with Fever with Thrombocytopenia

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Introduction

Thrombocytopenia is a disorder in which there are too few platelets in the blood. Platelets are small, disk-shaped cellular structures in the bloodstream that help the blood to clot. Thus thrombocytopenia is often characterized by excessive bleeding, including epistaxis and easy bruising. Thrombocytopenia can be diagnosed by a routine blood test. Thrombocytopenia arises for one of three reasons, the bone marrow may not produce enough platelets, too many platelets may be destroyed in the spleen, and thrombocytopenia can be caused by a variety of conditions.

Acute fever with thrombocytopenia (platelet count less than 150,000) is a common clinical problem in our medical wards. Febrile thrombocytopenia is the thrombocytopenia associated with fever. Diseases which commonly present with fever and thrombocytopenia are malaria, leptospirosis, rickettsial infections, septicemia, typhoid, borreliosis, arbovirus such as dengue or yellow fever, rodent-borne viruses such as Hanta and Lassa fever, human immunodeficiency virus (HIV), visceral leishmaniasis and TTP-HUS.[1]

Thrombocytopenia can occur as a complication of diseases such as leukemia or HIV infection. In some cases too many platelets are trapped and stored in the spleen leaving too few platelets in circulation. Treatment of thrombocytopenia depends on the type and cause of platelet deficiency. Thrombocytopenia in fever being a prognostic factor can predict the cause and thus helps in early diagnosis and treatment of the same, preventing further fatal outcome associated with it such as intracerebral bleed, hemorrhage into vital organs, shock and finally leading to death.

Majority of studies on adult with thrombocytopenia have focused on specific etiology or associated with some symptom like fever. On the other hand, Bhalara et al has taken different etiologies in consideration for one month duration study on adults during rainy season where mosquito transmitted diseases were the commonest cause.[2]

Though patients can initially present with simple fever in due course it can lead to unpredictable outcomes including death at times therefore the aim of the study is to analyze the etiological factors of thrombocytopenia, as early diagnosis and timely intervention prevents adverse outcomes and saves life.

Aims and Objectives

To study clinical and laboratory evaluation of patients with fever with thrombocytopenia

attending M.G.M Hospital Kamothe, Navi Mumbai

Material and Methods

This prospective observational study was conducted on 100 patients of fever with thrombocytopenia attending to M.G.M Hospital Kamothe, Navi Mumbai during the period from November 2016 to October 2018. Patients presenting with fever, temperature of more than 100° F, and thrombocytopenia i.e. platelet count of < 1.5 lakhs were enrolled in the study. Patients with known inherited causes for thrombocytopenia, patients on drugs causing thrombocytopenia, known Autoimmune causes for thrombocytopenia, HIV infection, leukemia's and myelodysplastic syndromes and other blood dyscrasias were excluded.

Methodology

Patients presenting to department of medicine in OPD or Emergency ward with complaints of Fever, and on investigation found to be having thrombocytopenia were screened for this study and those fulfilling Inclusion criteria were enrolled in the study after obtaining informed consent.

Patients were selected with the Simple random sampling method. Patients taken up for the study, and their details were entered in semi-structured proformas which included sociodemographic details, clinical history of patients, general and systemic examination, and Investigations. Further follow of patients in regard to their clinical prognosis and Investigations including platelet count were taken on regular interval, and depending on their clinical profile. Meanwhile, simultaneous records of diagnosis, treatment, prognosis were made as usual. Records were collected for 100 patients and then analyzed statistically through SPSS.

Statistical Analysis

All the collected data was entered in Microsoft Excel sheet and then transferred to SPSS software ver. 17 for analysis. Qualitative data was presented as frequency and percentages and analyzed using chi-square test. P-value < 0.05 was taken as level of significance

Results

Table no 1Demographic profile

Age group	Frequency	Percent
16 to 25 years	46	46
26 to 35 years	30	30
36 to 45 years	9	9
more than 45 years	15	15
Sex	Frequency	Percent
Female	19	19
Male	81	81
Clinical features	Frequency	Percent
Fever	100	100
Chills/Rigors	98	98
Vomiting	40	40
Headache	27	27
Cough/Breathlessness	18	18
Bleeding	19	19
Altered sensorium	5	5
Bleeding Manifestations	19	19

The most common age group amongst study population was 16 to 25 years (46%) followed by 26 to 35 years (30%), more than 45 years (15%) and 36 to 45 years (9%). There was male predominance (81%) amongst study population as compared to female (19%).

Fever (100%) was the most common clinical features amongst study population followed by chills/rigors (98%), vomiting (40%) and headache (27%). Bleeding manifestations was present in 19 % of study population. Splenomegaly and hepatomegaly was present in 7 % and 13 % of study population respectively.

Vivax Malaria (26 %) was the most common Peripheral smear findings amongst study population followed by Falciparum malaria (1%) and mixed malaria (1%). NS1 positive (47 %) was the most common diagnostic test for Dengue amongst study population followed by IgG positive (6%) and IgG &IgM (1%).

Leptospirosis and Widal test was positive in 13% and 2% of study population respectively.

Prothrombin time and INR was deranged in 48% and 36% of study population respectively

Most of the study population had platelet count of 50000-1lakh/cumm (39%) followed by 1-1.5 lakh/cumm (37 %) and less than 50,000/cumm (24%).

Acinetobacterial sp., E.Coli, Klebsiella and S. typhi was found in 1%, 1%, 1% and 1% of study population on blood culture findings respectively.

On USG Abdomen/Pelvis, hepatomegaly (17%) was the most common findings amongst study population followed by hepatosplenomegaly (15%) and splenomegaly (10%). On Bone marrow findings, Erythroid hyperplasia was observed in 1% of study population.

Dengue (53%) was the most common cause of thrombocytopenia amongst study population followed by Malaria (27%), Leptospirosis (13%), Septicemia (4%), Enteric fever (2%) and Dimorphic Anemia (1%)

Blood Product Transfusion was given in 16% of study population. Less than 10 days of hospital stay was observed in 94% of the study population while More than 10 days of hospital stay was observed in 6% of study population Eighty nine percent of the study population were alive while death was occurred in 11% of study population

Deranged prothrombin time was observed most commonly in dengue (45.8%) followed by malaria (37.5%), leptospirosis (6.3%), septicemia (4.2%) and enteric fever (4.2%) and the difference was statistically significant (P value – 0.04).

Deranged INR was observed most commonly in dengue (44.4%) followed by malaria (27.8%), leptospirosis (13.9%), septicemia (8.3%) and enteric fever (5.6%) and the difference was statistically insignificant (P value – 0.181).

Blood product transfusion requirement was observed most commonly in dengue (43.8 %) followed by leptospirosis (25.0%), septicemia (18.8%) and malaria (12.5%) and the difference were statistically significant (P value – 0.01).

Death requirement was occurred most commonly in dengue (36.40%) followed by leptospirosis (36.40 %) and septicemia (27.30 %) and the difference was statistically significant (P value – 0.0001)

Table no 2 Comparison of Final diagnosis with Prothrombin time amongst study population

| | | | Prothrombin time | | |
			Deranged	Normal	Total
Diagnosis	Dengue	Count	22	31	53
		%	45.8%	59.6%	53.0%
		%	2.1%	0.0%	1.0%
	Enteric fever	Count	3	0	3
		%	6.3%	0.0%	2.0%
	Leptospirosis	Count	3	10	13
		%	6.3%	19.2%	13.0%
	Malaria	Count	18	9	27
		%	37.5%	17.3%	27.0%
	Septicemia	Count	2	2	4
		%	4.2%	3.8%	4.0%
Total		Count	48	52	100
		%	100%	100.0%	100.0%

As seen in the above table, deranged Prothrombin time was observed most commonly in Dengue (45.8%) followed by Malaria (37.5%) , Leptospirosis (6.3%), septicemia (4.2%) and Enteric fever (6.3%) and the difference was statistically significant (P value – 0.04).

Table no 3 Comparison of Final diagnosis with INR amongst study population

			INR		
			Deranged	Normal	Total
Diagnosis	Dengue	Count	16	37	53
		%	44.4%	57.8%	53.0%
	Dimorphic Anemia	Count	0	1	1
		%	0.0%	1.6%	1.0%
	Enteric fever	Count	2	0	2
		%	5.6%	0.0%	2.0%
	Leptospirosis	Count	5	8	13
		%	13.9%	12.5%	13.0%
	Malaria	Count	10	17	27
		%	27.8%	26.6%	27.0%
	Septicemia	Count	3	1	4
		%	8.3%	1.6%	4.0%
Total		Count	36	64	100
		%	100%	100.0%	100.0%

As seen in the above table, deranged INR was observed most commonly in dengue (44.4%) followed by malaria (27.8%), leptospirosis (13.9%), septicemia (8.3%) and enteric fever (5.6%) and the difference was statistically insignificant (P value – 0.181).

Table no 4 Comparison of Final diagnosis with Blood Product Transfusion amongst study population

			Blood Product Transfusion		
			No	Yes	Total
Diagnosis	Dengue	Count	46	7	53
		%	54.8%	43.8%	53.0%
	Dimorphic Anemia	Count	1	0	1
		%	1.2%	0.0%	1.0%
	Enteric fever	Count	2	0	2
		%	2.4%	0.0%	2.0%
	Leptospirosis	Count	9	4	13
		%	10.7%	25.0%	13.0%
	Malaria	Count	25	2	27
		%	29.8%	12.5%	27.0%
	Septicemia	Count	1	3	4
		%	1.2%	18.8%	4.0%
Total		Count	84	16	100
		%	100.0%	100.0%	100.0%

As seen in the above table, Blood product transfusion requirement was observed most commonly in dengue (43.8%) followed by leptospirosis (25.0%), septicemia (18.8%) and malaria (12.5%) and the difference was statistically significant (P value – 0.01).

Table no 5 Comparison of Final diagnosis with Outcome amongst study population

			Outcome		Total
			Death	Alive	
Diagnosis	Dengue	Count	4	49	53
		%	36.40%	55.10%	53.00%
	Dimorphic Anemia	Count	0	1	1
		%	0.00%	1.10%	1.00%
	Enteric fever	Count	0	2	2
		%	0.00%	2.20%	2.00%
	Leptospirosis	Count	4	9	13
		%	36.40%	10.10%	13.00%
	Malaria	Count	0	27	27
		%	0.00%	30.30%	27.00%
	Septicemia	Count	3	1	4
		%	27.30%	1.10%	4.00%
Total		Count	11	89	100
		%	100.00%	100.00%	100.00%

As seen in the above table, death occurred most commonly in dengue (36.40%) and leptospirosis (36.40%) each and septicemia (27.30%) and the difference was statistically significant (p value – 0.0001). The common causes of death were dengue hemorrhagic fever leptospirosis with ARDS and septicemia with shock.

Discussion

Thrombocytopenia (TCP) refers to a reduction in platelet count below 1.5lakh/microlitre.[3] It is the commonest platelet abnormality encountered in clinical practice with variable clinical expression. With the widespread use of automated cell counters clinicians in any field may encounter TCP. The symptomatology may vary greatly and the underlying cause may be either inconsequential or life threatening. [4] In a tropical country like India infectious causes predominate and are usually associated with fever.[5] TCP may give a clue to presence of infections like malaria, dengue, leptospirosis and viral infections.

Febrile thrombocytopenia is a distinct clinical entity, commonly encountered in infectious diseases. A number of infections such as malaria, dengue fever, scrub typhus, leptospirosis, chickungunya, enteric fever, bacterial and fungal sepsis as well as certain other viral infections result in thrombocytopenia. The varied etiological profile and unpredictable clinical outcome often poses a diagnostic as well as therapeutic challenge to clinicians.

Age group

In the present study, 16 to 25 years (46%) was the most common age group amongst study population followed by 26 to 35 years (30%), more than 45 years (15%) and 36 to 45 years (9%). This findings is in agreement with the study conducted by Yasmeen Khatib et al., in which there were 68 cases (22.67%) seen in the 21-30 year age group followed by 58 patients in the 31-40 year age group.(19.33%).[6] This findings is also in agreement with the study conducted by Smita Masamatti et al ., in which the commonest age group affected was between 18 to 36 years (48.27%), the reason for this increased incidence in males and younger age group in the given locality has been attributed to the prolonged outdoor activities and increased chances of exposure to mosquitoes and also majority of the women being homemaker.[7] In another study by Shah et al maximum cases of thrombocytopenia were also found in the 21-30 years age group and male preponderance was seen as in our study.[8]

Sex

In the present study, there was male predominance (81%) amongst study population as compared to female (19%). This findings is in agreement with the study conducted by Yasmeen Khatib et al., in which there were 176(58.67%) males and 124(41.33%) females. [6] This findings is also in agreement with the study conducted by Bhalara, et al in which out of 412 cases (236 male and 176 female patients).[2] According to another study by Badvi A. J. et al, male to female ratio was 64:36 and 77% of patients were in age group under 10 years.[9] Similar sex distribution was seen in certain local and international studies.[10-12]

Clinical Features

In the present study, Fever (100%) was the most common Clinical features amongst study population followed by Chills/Rigors (98%), Vomiting (40%) and Headache (27%). This findings is in agreement with the study conducted by Yasmeen Khatib et al., in which The main presenting features in patients with TCP were fever 205 cases (68.3%).[6] This findings is also in agreement with the study conducted by Bhalara, et al in which fever associated with thrombocytopenia was found in 327 (79.3%).[2] In another study by Ahmed S et al study,16 frequently noted clinical features included fever (97%), vomiting (68%), abdominal pain (68%) and rashes (65%). Gastrointestinal bleeding (61%) and epistaxis (26%) were commonest haemorrhagic manifestations.[11]

In the present study bleeding manifestations were present in 19 % of study population. This findings is also seen in a study conducted by Yasmeen Khatib et al., in which The clinical presentation

with bleeding tendencies was seen in 70 cases (23.3%).[6] Nair et al [4] have reported bleeding manifestations in 41.3% of their cases while Shah et al have reported them in 30% of their cases.[8] Signs of bleeding were reported in 24% children and in 23% adults by Kuhne T et al.[10]

Examination findings

In the present study, Splenomegaly and Hepatomegaly was present in 7 % and 13 % of study population respectively. This findings is in agreement with the study conducted by Yasmeen Khatib et al., in which hepatomegaly 48 cases (16%), splenomegaly 46 cases (15.3%).[16]

Peripheral smear findings

In the present study, Vivax Malaria (26 %) was the most common Peripheral smear findings amongst study population followed by Falciparum Malaria (1%) and Mixed malaria (1%).This findings is in agreement with the study conducted by Guruprasada Shetty et al study,30 Plasmodium vivax found in 66%, Plasmodium falciparum in 16% and mixed in 18% of cases.[13] This findings is in agreement with the study conducted by Naveen Kulkarni et al., vivax malaria, falciparum and mixed infections were noted in 53.2%, 26.6% and 19 % cases respectively.[14]

Platelet count

In the present study, most of the study population had Platelet count of 50000-1lakh/cumm (39%) followed by 1-1.5 lakh/cumm (37 %) and less than 50,000/cumm (24%).This findings is in agreement with the study conducted by Bhalara, et al in which out of 109 patients, 62 (56.8%) had platelet count between 50,000 and 1,00,000, followed by 28 (25.7%) patients who had count between 20,000 and 50,000. [2] This findings is in agreement with the study conducted by Yadav et al., most of the study population had platelet distribution 50,001-1, 00,000/cumm was seen in 53.8% cases.[15] Similar results (56.8%) were obtained in Nair PS et al study for this platelet distribution range.[4]

Final diagnosis

In the present study, Dengue (53%) was the most common cause of thrombocytopenia amongst study population followed by Malaria (27%), Leptospirosis (13%), Septicemia (4%), and Enteric fever (3%). This findings is in agreement with the study conducted by Bhalara, et al in which the most common etiology responsible for newly diagnosed thrombocytopenia in adult patients was found to be dengue/dengue-like fever (28.6%).[2] This findings are also seen in the study conducted by Smita Masamatti et al., in which the commonest etiology for fever with thrombocytopenia was Dengue (48.28%), followed by septicemia (19.83%), typhoid (15.52%). It was more common among males (64.82%) than in females (35.18%).[7] In another study by Badvi A. J. et al study, enteric fever contributed to about 5% of cases of febrile thrombocytopenia which is similar to the present study.[9] Dengue and malaria were the common causes due to the higher prevalence of these infections during the study period (October), which may be the reason for variation between different studies. The pathogenesis of thrombocytopenia in dengue fever is not clearly understood. Increased peripheral destruction of antibody coated platelets is strongly suspected as the possible mechanism. Other modes include acute bone marrow suppression leading to amegakaryocytic condition, mild DIC like presentation and enhanced platelet destruction by the reticuloendothelial system.[16]

Morbidity

In the present study, Blood Product Transfusion requirement was observed most commonly in Dengue (43.8 %) followed by Leptospirosis (25.0%), septicemia (18.8%) and Malaria (12.5%) and the difference was statistically significant (P value – 0.01).

Blood Product Transfusion was given in 16% of study population. In a study by Anubha Sharma blood product transfusion was given in 38% of cases.[17]

In the present study, 94% of the study population had Less than 10 days of hospital stay while More than 10 days of hospital stay was observed in 6% of study population

Final outcome

In the present study, 89% of the study populations were Alive while death was occurred in 11% of study population. In the study by Lohitashwa et al septicemia accounted for 78% and dengue for 22% of mortality.[18] Kumar et al study on fever with thrombocytopenia found 9.47% mortality where 83.33% were due to septicemia with multiorgan dysfunction and 16.67% were due to complicated malaria.[19]

Coagulation profile vs Final diagnosis

In the present study, deranged Prothrombin time was observed most commonly in Dengue (45.8%) followed by Malaria (37.5%), Leptospirosis (6.3%), septicemia (4.2%) and Enteric fever (6.3%) and the difference was statistically significant (P value – 0.04). similarly in the study by Tejas N. Modi et al., Viremia 241(61.32%) constitutes the commonest a etiology of febrile thrombocytopenia of which 220(55.98%) were of dengue fever and 21(5.34%)viral infection other than dengue, followed by Malaria 102(25.95%), Septicemia 21(5.34%), Megaloblastic anemia 11(2.79%), Hematological malignancy 11(2.79%) and Enteric fever 6(1.58%). [20]

In the present study, deranged INR was observed most commonly in dengue (44.4%) followed by malaria (27.8%), leptospirosis (13.9%), septicemia (8.3%) and enteric fever (5.6%) and the difference was statistically insignificant (P value – 0.181). Many studies have shown an association of dengue with TCP which if severe can lead to bleeding tendency.[21-23] Leptospirosis can also present with TCP.[24, 25]

Outcome vs Final diagnosis

In the present study, Death was occurred most commonly in Dengue (36.40%) followed by Leptospirosis (36.40 %) and septicemia (27.30 %) and the difference was statistically significant (P value -0.0001). The common causes of death were Dengue Hemorrhagic Fever Leptospirosis with ARDS, septicemia with shock

Conclusion

Dengue is the most common diagnosis made in adult patients who present with fever and are detected to have thrombocytopenia at admission followed by malaria and leptospirosis. Most of the study population had Platelet count of 50000-1lakh/cumm followed by 1-1.5 lakh/cumm and less than 50,000/cmm. In malaria, P. vivax was most common followed by P. falciparum infection and then mixed infection. Nineteen percent of patients with thrombocytopenia tend to have bleeding manifestations, most common being the bleeding from gums. Dengue was the most common cause of thrombocytopenia followed by Malaria, Leptospirosis and Septicemia. Blood Product Transfusion was needed in 16% of the patients.

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