A Cross-Sectional Study of Clinical Profiles and Complications Associated with Fever with Thrombocytopenia

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ABSTRACT

BACKGROUND

Fever is the commonest cause of thrombocytopenia that narrows the differential diagnosis and management of fever. The complexity of thrombocytopenia and its control can also be determined through fever. Lack of proper surveillance system and limited laboratory services pose a definite challenge for a perfect diagnosis leading to case management primarily based on clinical manifestations

METHODS

A cross-sectional study was conducted on 90 patients attending outpatient department of Vinayaka Missions Kirupananda Variyar Medical College & Hospitals, during the period of April 2017 to September 2017 (6 months). In patients with fever with thrombocytopenia, a careful history was recorded, general physical examination, laboratory and technical investigation reports were noted down from regular investigations. Culture sensitivity and serology were considered as primary outcome variables. The continuous data was expressed as mean ± standard deviation (SD) and for independent sample "t" test was used to compare the data. A probability value ("P" value) of ≤ 0.05 at 95 % confidence interval was considered as statistically significant using Statistical Package for the Social Sciences (SPSS).

RESULTS

The mean age was 44.73 ± 21.18 years in the study population. 39 (43.33 %) were males and 51 (56.67 %) were females. The average period of stay in the hospital was 8.84 ± 5.73 days; the most common chief complaint was chills & rigors seen in 65 (72.22 %) patients. The most commonly observed comorbidity in the patients was diabetes mellitus. The mean and SD of platelet count was 91522.22 ± 32265.13 per µL. 21 (23.33 %) people had dengue. The mean platelet count at discharge was 192215.19 ± 49481.85 per µL.

CONCLUSIONS

The commonest cause is infection, for fever with decreased platelet count. A significant number of cases of febrile thrombocytopenia were diagnosed as sepsis in the present study.

KEYWORDS

Infection, Dengue, Septicaemia, Petechiae / Purpura, Spontaneous Bleeding, Fever

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BACKGROUND

Fever is defined as an elevation of the body temperature above the normal circadian range as the result of a change in the thermoregulatory centre located in the anterior hypothalamus.[1] An a.m. temperature of > 37.2° C (> 98.9° F) or a p.m. temperature of > 37.7° C (> 99.9° F) would define a fever. The normal daily temperature variation is typically 0.5° C (0.9° F).[2]

Characteristics of probable severe fever with thrombocytopenia syndrome patients: a perspective study from Pakistan febrile patient with thrombocytopenia is commonly encountered by physicians especially during monsoon and peri monsoon period.[3] Thrombocytopenia is defined as platelet count < 1,50,000 / µL. This is due to decreased production, increased destruction (immunogenic and non-immunogenic), and increased sequestration in spleen. Of these infections being the commonest cause of thrombocytopenia.[4] Infections like dengue, leptospirosis, malaria, typhoid, military TB, HIV, septicaemia is some of the common causes of fever with thrombocytopenia.[5]

In 2005, an outbreak of patients with acute febrile illness having in common gastrointestinal (GI) symptoms, thrombocytopenia, and leukopenia were identified in China.[6] Due to the lack of laboratory confirmation, these patients were diagnosed as "Probable Human Granulocytic Anaplasia" on the basis of clinical constellation of symptoms.[7] In Pakistan, febrile illness with thrombocytopenia is generally seen after monsoon season.[8] dengue, malaria, typhoid, chikungunya and Crimean-Congo haemorrhagic fever (CCHF), and so on are the common etiological agents in the country. During 2017, a number of patients with fever and thrombocytopenia were reported at Rawalpindi Medical University (RMU).[9]

Lack of proper surveillance system and limited laboratory services pose a definite challenge for a perfect diagnosis leading to case management primarily based on clinical manifestations. Hence, a precise systematic approach is to be conducted with focus on aetiology of fever with decreased platelet count which eventually helps in highlighting the diagnosis. Prompt recognition of the underlying condition and treating it with blood transfusion to increase platelet count is required to prevent deadLy consequences.

With this background the present study was undertaken to determine the clinical profile and complications of fever with thrombocytopenia by evaluating clinical and laboratory profile of fever with thrombocytopenia, identify its cause and complications associated with it. The study was conducted to determine the clinical profile and complications associated with fever with thrombocytopenia.

METHODS

A cross-sectional study was conducted on 90 patients selected through convenience sampling, who were presented to emergency room of Vinayaka Missions Kirupananda Variyar Medical College & Hospitals, during the period of April 2017 to September 2017 (6 months). We prospectively collected the data on a series of 90 patients with fever with thrombocytopenia. After obtaining permission from ethical committee of the institution and informed consent from patients with fever with thrombocytopenia; all IP patients of both sexes above 18 years with history of fever with low platelet count were included in the study.

Exclusion Criteria

1. Patients with thrombocytopenic purpura.
2. Patients diagnosed to have haematological disorder, malignancy, on chemotherapy and immune suppressants.
3. Patients with platelet disorders and dysfunction.
4. Patients on antiplatelet drugs and other drugs which will cause thrombocytopenia.
5. Patients with chronic liver disease including cirrhosis of liver.

A detailed case history, general physical examination of various systems was recorded, and a routine investigation and specific & special investigations were done when required. The patients diagnosed with fever were given treatment accordingly and lab investigation for platelet count was done during discharge and they were not followed thereafter. A detailed history, general physical examination and lab investigations were recorded continuously and once the diagnosis was finalised, treatment was given for specific and symptomatic causes (mechanical ventilations, haemodialysis etc.); for bleeding conditions platelet transfusions was made.

Statistical Analysis

Investigation, culture sensitivity and serology were considered as primary outcome variables. Age, gender, total number of hospital stays, symptoms, comorbidities, vitals, and general examination were primary explanatory variables. The data obtained was coded and entered into Microsoft Excel worksheet and later fed into SPSS software. Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. The categorical data was expressed as rates, ratios and proportions and comparison and was done using chi-square test. The continuous data was expressed as mean ± standard deviation (SD) and for independent sample "t" test was used to compare the data. A probability value ("P" value) of ≤ 0.05 at 95 % confidence interval was considered as statistically significant.

RESULTS

A total of 90 subjects was included in the final analysis. The mean age was 44.73 ± 21.18 in the study population. Among the study population, 39 (43.33 %) participants were

male and remaining 51 (56.67 %) participants were female. The average period of stay in the hospital was 8.84 ± 5.73 days in the study population. During the study, most common chief complaint was chills & rigours seen in 65 (72.22 %) people. The most commonly observed comorbidity in the patients was diabetes mellitus.

	Parameter	Summary
	Age (mean ± SD)	44.73 ± 21.18 (range 18 to 85)
Gender	Male	39 (43.33 %)
	Female	51 (56.67 %)
Total number of days in hospital (mean ± SD)		8.84 ± 5.73 (range 0 to 29)
Symptoms	Myalgia / joint pain & swelling	48 (53.33 %)
	Chills & rigour	65 (72.22 %)
	Rashes	29 (32.2 %)
	Foci of infection	27 (30.0 %)
	Bleeding	21 (23.3 %)
Comorbidities	Diabetic mellites	42 (46.67 %)
	Coronary atherosclerotic heart disease	15 (16.7 %)
	Chronic kidney disease	4 (4.4 %)
	Systemic arterial hypertension	27 (30 %)
	Acute renal failure	6 (6.7 %)
	Dilated cardiomyopathy	1 (1.1 %)
	Chronic obstructive pulmonary disease	1 (1.1 %)

Table 1. Summary of Demographic Variables and Comorbidities (N = 90)

	Parameter	Summary
Vitals	Systolic blood pressure in mm of hg (mean ± SD)	126.44 ± 24 (range 70 to 180)
	Diastolic blood pressure (mean ± SD)	79.11± 13.95 (range 50 to 110)
	Pulse rate in 1 minute (mean ± SD)	105.44 ± 16.35 (range 78 to 142)
	Respiratory rate in 1 minute (mean ± SD)	23.38 ± 6.62 (range 3 to 38)
	Temperature in Fahrenheit (mean ± SD)	102.49 ± 0.9 (range 100.4 to 104.2)
	Oxygen saturation in % (mean ± SD)	95.52 ± 5.34 (range 64 to 99)
GCS	Eye (4) / verbal (5) motor (6) = (/ 15) (mean ± SD)	14.11 ± 2.42 (range 3 to 15)
General Examination	Pallor	44 (48.89 %)
	Icterus	15 (16.7 %)
	Clubbing	13 (14.4 %)
	Cyanosis	2 (2.2 %)
	Lymphadenopathy	22 (24.4 %)
	Pedal oedema	36 (40 %)
Gastrointestinal System	Normal	38 (42.2 %)
	Abnormal	49 (54.4 %)
	Non-gastrointestinal system	3 (3.3 %)
Respiratory System	Normal	44 (48.89 %)
	Abnormal	3 (3.33 %)
	Creps	33 (36.67 %)
	Creps / ronchi	7 (7.78 %)
	Ronchi	3 (3.33 %)
Cardiovascular System	Normal	78 (86.7 %)
	Abnormal	12 (13.3 %)
Central Nervous System	Normal	78 (86.7 %)
	Abnormal	12 (13.3 %)

Table 2. Summary of Vital and Systematic Parameters (N = 90)

The mean systolic blood pressure recorded during the study period was 126.44 ± 24 in the study population. The mean diastolic blood pressure was 79.11 ± 13.95 the mean pulse rate was 105.44 ± 16.35. The mean respiratory rate was 23.38 ± 6.62, the mean temperature was 102.49 ± 0.9 F. The mean oxygen saturation in % was 95.52 ± 5.34 majority (48.89 %) of the subjects had general sign of pallor. 40 % patients had pedal oedema, (24.2 %) patients had lymphadenopathy, (16.7 %) patients had icterus, (14.4 %) patients had clubbing and (2.2 %) patients had cyanosis.

The mean and SD of haemoglobin was 10.03 ± 2.75, WBC count was 14813.33 ± 8035.11 and platelet count was 91522.22 ± 32265.13. The mean values of serum creatinine, urea, serum bilirubin, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), activated partial thromboplastin time (APT) are shown in the table 3. Among the study population, all of them 90 (100 %) had normal bleeding time, normal clotting time & normal prothrombin time. Majority (62.22 %) of the subjects had normal blood culture, urine culture and pus culture. 21 (23.3 %) patients had NS1 antigen of dengue, 16 (17.8 %) had IgG and 16 (17.8 %) had IgM. Majority (13.3 %) of the subjects had Widal of leptospirosis. The proportion of participants who had HIV, IgG and IgM was 2.2 % each.

	Parameter	Summary
CBC Parameter	Haemoglobin in g / dL (mean ± SD)	10.03 ± 2.75 (range 5.5 to 16.4)
	Total WBC count (cubic mm) (mean ± SD)	14813.33 ± 8035.11 (range 4200 to 3600)
	Platelet count (cubic mm) (mean ± SD)	91522.22 ± 32265.13 (range 27000 to 144000)
Urine Routine	Normal	53 (58.89 %)
	Pus Cells	26 (28.89 %)
	Pus cells / RBC	1 (1.11 %)
	Red blood cells	10 (11.11 %)
Peripheral Smear for MP	Positive	5 (5.56 %)
	Normal	85 (94.44 %)
RFT Parameter	S. Creatinine (mg / dL) (mean ± SD)	1.4 ± 0.62 (range 0.8 to 4.1)
	B. Urea (mg / dL) (mean ± SD)	39.71 ± 21.59 (range 15 to 146)
LFT Parameter	S. Bilirubin (mg / dL) (mean ± SD)	1.26 ± 0.61 (range 0.7 to 4.4)
	SGOT (AST) (mean ± SD)	55.34 ± 37.07 (range 16 to 186)
	SGPT (Alt) (mean ± SD)	66.77 ± 47.67 (range 22 to 240)
	Activated pro thrombin time in seconds (mean ± SD)	43.67 ± 16.57 (range 26 to 94)
Blood Culture - Culture & Sensitivity	Normal	56 (62.22 %)
	Abnormal	34 (37.77 %)
Urine Culture	Normal	81 (90.00 %)
	Abnormal	9 (10 %)
Pus Culture	Normal	68 (75.56 %)
	Abnormal	22 (24.44 %)
Dengue	NS1 Antigen	21 (23.3 %)
	IgG	16 (17.8 %)
	IgM	16 (17.8 %)
Leptospirosis	IgG	2 (2.2 %)
	IgM	2 (2.2 %)
	HIV	2 (2.2 %)
	WIDAL	12 (13.3 %)

Table 3. Summary of Outcome of Parameters (N = 90)

	Parameter	Summary
Diagnosis	Dengue	21 (23.33 %)
	Leptospirosis	2 (2.22 %)
	Malaria	6 (6.67 %)
	PUO	11 (12.22 %)
	Sepsis	38 (42.22 %)
	Typhoid	12 (13.33 %)
Drugs & IV Fluids / Others	FAAS	6 (6.67 %)
	FAIPS	6 (6.67 %)
	FAIS	31 (34.44 %)
	FAS	25 (27.78 %)
	FFPS	15 (16.67 %)
	FS	7 (7.78 %)
	Platelet transfusion (mean ± SD)	1.87 ± 3.79 (range 0 to 14)
Outcome	Expired	11 (12.22 %)
	Good	79 (87.78 %)
	Platelet count at discharge (mean ± SD) (N = 79)	(192215.19 ± 49481.85 range 126000 to 340000)

Table 4. Summary of Diagnosis and Treatment Parameters (N = 90)

Among the study population, 21 (23.33 %) patients had dengue. The number of leptospirosis, malaria, pyrexia of

unknown origin (PUO), sepsis and typhoid were 2 (2.2 %), 6 (6.67 %), 11 (12.22 %), 38 (42.22 %) and 12 (13.33 %) respectively, 31 were treated with fluids, antibiotics, inotropes, and supportive care (FAIS), 25 were treated with fluids, antibiotics and supportive care (FAS), 15 were treated with fluids, fresh frozen plasma, platelet transfusion and supportive care (FFPS), 7 were treated with fluids and supportive care (FS), 6 were treated with fluids, antibiotics, antimalarial (artesunate / artemether / chloroquine) and supportive care (FAAS), 6 were treated with fluids, antibiotics, inotropes, platelet transfusion and supportive care (FAIPS) 11 (12.22 %) had expired and 79 (87.78 %) had good outcome. The mean platelet count at discharge in seconds was 192215.19 ± 49481.85 in the study population, minimum level was 126000 and maximum level was 340000.

DISCUSSION

In our study we found that only 23 % of the population suffered from dengue. However, the number of sepsis cases were around 42 %. These results are in contrast with most of the previous studies. Studies by Saini et al, Gandhi et al and Modi et al found that Dengue fever was the most common aetiology for febrile thrombocytopenia.[10-12] A similar study done in Coimbatore by P Vishnuram stated that Out of 100 patients only 34 were dengue positive, 66 were dengue negative.[13]

A study was conducted by Nair PS et al[14] (2003) at St. Stephen's Hospital, New Delhi, for period of one and half years. A total of 109 cases (76 male, 33 female patients) were studied with the same criteria as in our study. In present study 39 were males and 51 were female. In Nair study septicaemia with 29 cases was the leading cause of fever associated with thrombocytopenia contrast to present study with 38 cases of sepsis.

In Srinivas study[15] malaria with 41 cases was the leading cause of fever associated with thrombocytopenia which is in contrast to present study where only 6 cases of malaria were seen. In the present study Dengue with 21 cases and sepsis 38 cases as leading cause of fever associated with thrombocytopenia.

Infections (100 %) was the established diagnosis in the present study when compared to Nair study in which infection (68 %) was accompanied by haematological conditions (15 %). In Srinivas study infections (100 %) were the established diagnosis. there were 6 cases of malaria but a study done by M.P Gondhali et al[16] showed 17 cases compared to Nair study there were 41 cases of malaria where species were identified. In the present study species was not identified like Nair and Gondhali et al.[16]

Platelet counts in the range of 27000 - 144000 was seen in 15 (15 %) cases in our study as compared to 28 (25.7 %) in the studies by Nair et al respectively. In the present study, > 50000 / µL was the range for the distribution of cases. In Nair study, during the course of follow up there was increase in platelet count in 63.3 % cases and decrease in counts was seen in 7.3 % cases, which was in contrast to present study which showed increase in platelet count in all cases who recovered at the time of discharge. As the present study considered only infectious diseases, decrease in platelet count was not observed. In present study out of 100 patients 15 % had thrombocytopenic sign accounting for 15 % which is in contrast to Nair study and Srinivas study where 41.3 % and 49 % of patients showed signs of thrombocytopenia.

In our study the diagnosis of sepsis was made based upon the criteria given by surviving sepsis. According to the Surviving Sepsis Guidelines, a sepsis diagnosis requires the presence of infection, which can be proven or suspected, and 2 or more of the following criteria: However, the cause of such discrepancy is unknown. We could attribute the low incidence of dengue in our centre to the low mosquito levels. The cause of thrombocytopenia in these patients could be attributed to sepsis. However, thrombocytopenia triggers a knee jerk reaction which leads to screening for dengue, malaria, typhoid etc. The results of this study signify the need for screening of sepsis in these patients. Although the platelet count in our patients was more than 10000 in most cases the presence of bleeding could be due to administration of NSAIDs.

CONCLUSIONS

The study concluded that fever with low platelet count was very difficult to diagnose as it is a hidden presentation of common diseases rather than rare diseases and infection being one of the most common causes of fever with thrombocytopenia. A significant number of cases of febrile thrombocytopenia were diagnosed as sepsis in the present study, also unjustified use of nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids must be avoided.

Limitations

Sample size was small and hence the results cannot be generalised. This was a hospital-based study, so can affect the generalisability on healthy population. We did not identify the species for malaria. Bone marrow evaluation was not done which would have given more detailed diagnosis of haematological disorders. Further research with large sample and population-based studies has to be carried.

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