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ORIGINAL RESEARCH

A Study of Correlation of Vitamin B12 Levels in Patients of Febrile Thrombocytopenia

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Abstract

Introduction: Acute fever with thrombocytopenia is commonly encountered by physicians especially during monsoon and perimonsoon period. Infection is the most common cause of fever associated with thrombocytopenia. Commonly includes dengue, malaria, scrub typhus, rickettsia and other certain viral infections. Since Vitamin B12 is essential for hemopoiesis, this study was intended to know the correlation of vitamin B12 levels with the febrile thrombocytopenia.

Methods: This is a prospective observational study done in 113 patients presented with acute febrile illness with thrombocytopenia. Detailed clinical and laboratory evaluation was done to know the etiology and vitamin B12 levels is assessed.

Results: Among 113 patients, 72 were male and 41 were female. Undetermined fever was the most common cause of febrile thrombocytopenia followed by dengue. 28 subjects were Vitamin B12 deficient. Severity of thrombocytopenia was more in subjects of Vitamin B12 level <200 pg/L. Number of RDP transfused was more in subjects with vitamin B12<200 pg/L group. Mean duration of hospital stay was more in Vitamin B12 deficient subjects. There was no correlation with mortality with vitamin B12 level.

Conclusion: This study suggests that Vitamin B12 deficiency associated with more severe thrombocytopenia, prolonged hospital stay and increased RDP transfusion in patients of acute febrile thrombocytopenia.

Keywords: febrile thrombocytopenia, vitamin B12, undetermined fever, dengue, RDP transfusion.

Introduction

Fever is defined as an elevation of the body temperature above the normal circadian range as the result of a change in the thermoregulatory center located in the anterior hypothalamus. An AM temperature of >37.2°C (98.9°F) or a P.M. temperature of >37.7°C (99.9°F) would define "fever".[1]

The pattern of fever and associated localizing signs and symptoms helps in differential diagnosis of fever. Fever associated with thrombocytopenia further narrows the differential diagnosis of the clinical entity. Thrombocytopenia is defined as platelet count <1,50,000/µl. Though thrombocytopenia in various diseases is common, it is fortunate that potentially fatal bleeding due to thrombocytopenia is rare. The mechanism of thrombocytopenia are impaired platelet production, accelerated platelet destruction(immunogenic and non-immunogenic) or increased sequestration in spleen.[2,3] Thrombocytopenia correlates with mortality and morbidity in various febrile illness, serial monitoring of platelet counts has prognostic value,

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and highlights the importance of thrombocytopenia in various febrile disorders.[4]
Fever with thrombocytopenia consists of occult presentations of the common diseases rather than the rare diseases. Infection is the commonest cause of fever with thrombocytopenia. Among infections, dengue fever is the commonest cause.[5] Other common causes of acute febrile illness with thrombocytopenia are malaria, septicemia, leptospirosis, enteric fever, chicken gunya, scrub typhus fever and others, Etilogies for febrile thrombocytopenia varies according to geographical areas, because some diseases are endemic in some geographical regions. Febrile thrombocytopenia commonly presents as symptoms/ signs of underlying condition and sometime with bleeding manifestations. Treatment of underlying condition will lead to rapid improvement in platelet count with complete clinical recovery. Mortality also depends on the concomitant involvement of other organs leading to multiorgan dysfunction.[6]
Indian population is deficient in vitamin B12 level because of vegetarian habit and lack of a balanced diet. Vitamin B12 required for the hematopoiesis. Platelet production could be reduced to 10% in vitamin B12 deficiency reflecting ineffective thrombopoiesis and platelet may be functionally abnormal.[7,8]
We have taken this study with the presumption that there may be other factors that may contributing to the thrombocytopenia and its slow recovery, during acute hematological stress, from which one of them is serum Vitamin B12. Identification and correction of this contributory factor may probably cut down the duration of hospitalization of patients. Hence there is a need for study of correlation of Serum Vitamin B12 levels in patients of acute febrile illness with thrombocytopenia.

Material and methods

We have conducted this prospective observational study at Karnataka Institute of Medical Sciences, Hubballi, Karnataka, India from December 2019 to November 2021 after taking clearance from the Ethical committee. 113 patients of age more than 14 years and presented with acute febrile illness of less than 1 week duration with thrombocytopenia at presentation are included in this study. Patients with congenital platelet disorders, hematological disorders/malignancy or on treatment with chemotherapy, immunosuppressive agents, drugs causing thrombocytopenia and on Vitamin B12 supplements in last 3 months are excluded from this study.
Detailed clinical history and complete examination were noted. All patients were subjected to complete blood count, Peripheral smear study for malarial parasite , Dengue serology test, Widal test, Weil Felix test, Liver function test, Renal function test, Urine routine, Chest X-ray, blood culture, Ultrasound abdomen. Vitamin B12 level is assessed by chemiluminescence method in all patients. All patients were given supportive treatment at admission and specific treatment is given after definitive diagnosis. Patients were followed up for their duration of hospital stay and outcomes were analyzed.

Statistical Analysis

Data were entered into Microsoft Excel and statistical analysis was carried out in SPSS software version 17.0. Association of variables with B12 levels were done with chi square test. A p-value of <0.05 was considered as statistically significant.

Results

Of all 113 patients with febrile thrombocytopenia, 72(63.7%) were men and the remaining 41(36%) were women. Majority of the patients 52(46%) belonged to 21-30 years of age. 23(20.3%) of the patients were more than 40 years of age and another 20.4% of patients were 20 years and less. 88(77%) were consuming non-vegetarian or mixed dietary pattern and 25(22%) were consuming only vegetarian diet. 53(46.9%) patients recruited for this study

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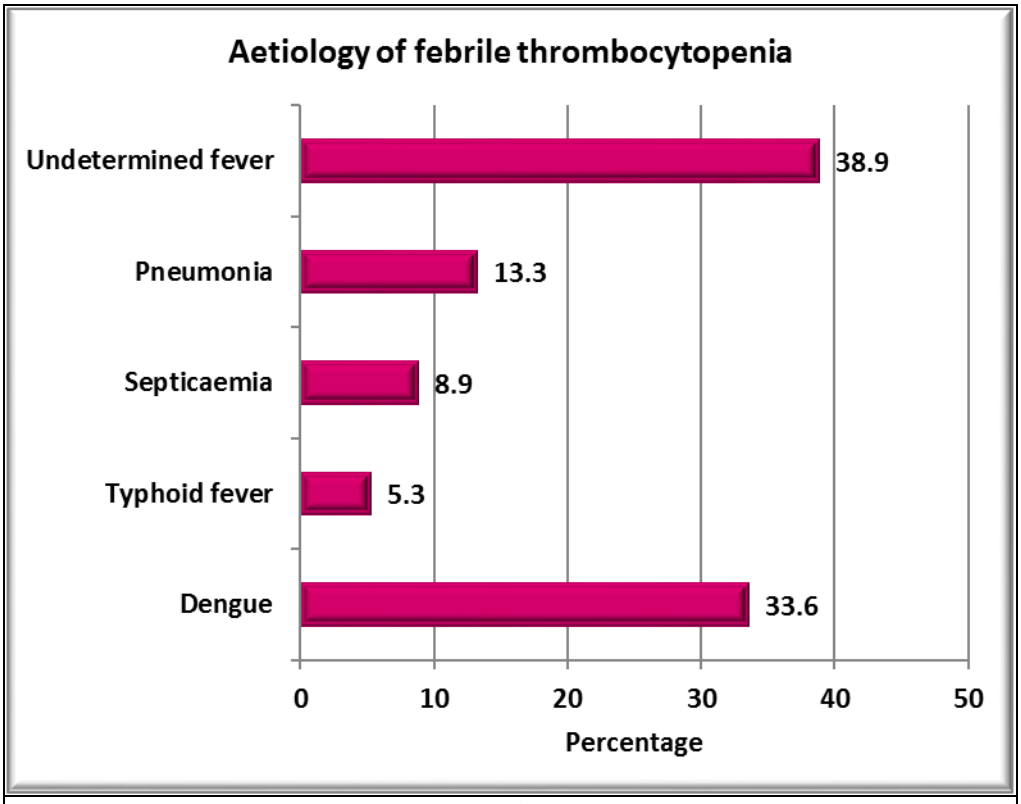
had moderate form of thrombocytopenia with platelet count of 50000-1 lakh/µl, 30(26.6%) had severe form of thrombocytopenia (20,000-50,000/µl), 20(17%) had mild thrombocytopenia (1 lakh- 1.5 lakh/µl) and 10(9%) patients had very severe thrombocytopenia (<20,000/ µl) at admission.

The present study showed that undetermined fever was the etiology in 44(38.9%) patients. It is followed by dengue in 38(33.6%) patients, pneumonia contributed for 15(13.3%)cases, septicemia was seen in 10(9%) and the remaining 6 (5.3%) patients had typhoid fever. Almost half of participants (49.6%) in our study had a sufficient vitamin B12 level of >300pg/L, one fourth (25.7%) had borderline deficient Vitamin B12 level of 201-300pg/L. 23 (20.4%) of patients had B12 level of 101-200pg/L and 5 (4.4%) had <100pg/L of vitamin B12. Thus the present study includes 28(24.8%) vitamin B12 deficient cases. 27(23.9%) patients had 2 days of hospital stay and 19(16.8%) had taken more than 6 days. Majority of our patients, 47(41.6%) hospital stay was in a range of 3-4 days. 20 patients (17.7%) had been admitted for 5-6 days.

Patients who had a vitamin B12 level of <100 pg/L, 60% had severe thrombocytopenia(20,000-50,000/µl) and 40% had moderate thrombocytopenia(50,000-1lakh/µl). In patients with vitamin B12 101-200 pg/L B12 groups, 26% had a very severe thrombocytopenia; the severe thrombocytopenia was seen in 47.8%, moderate thrombocytopenia in 8%, and mild thrombocytopenia in 17% of patients.

RDP requirement was more in Vitamin B12<200 pg/L group which is statistically significant. Duration of hospital stay was highest in Vitamin B12<100 pg/L group with mean duration of hospital stay of 6.2 days as compared to other groups and it was statistically significant (p-value = 0.005).Out of 8 died patients, 3 had Vitamin B12 deficiency.



Graph 1

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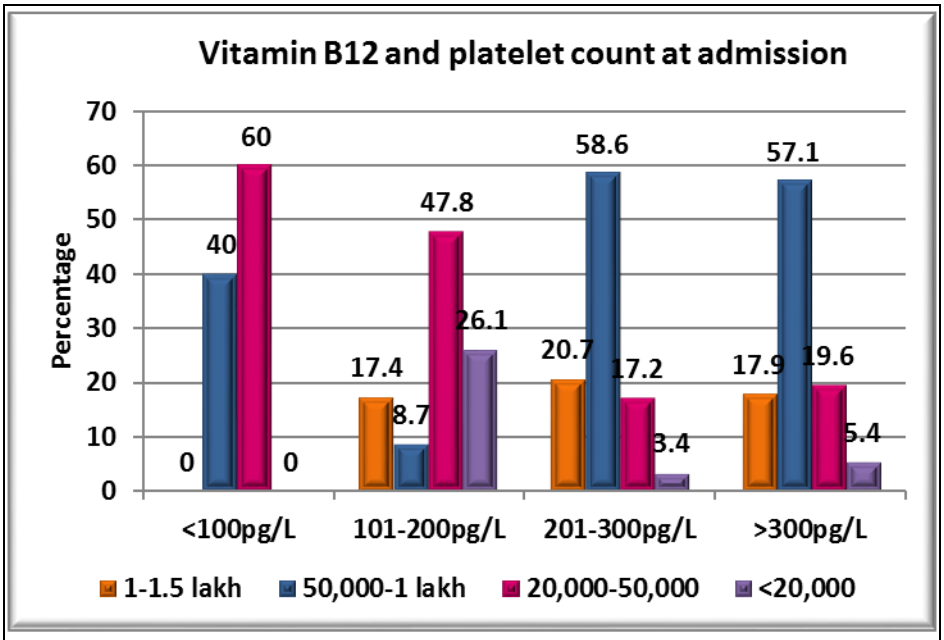
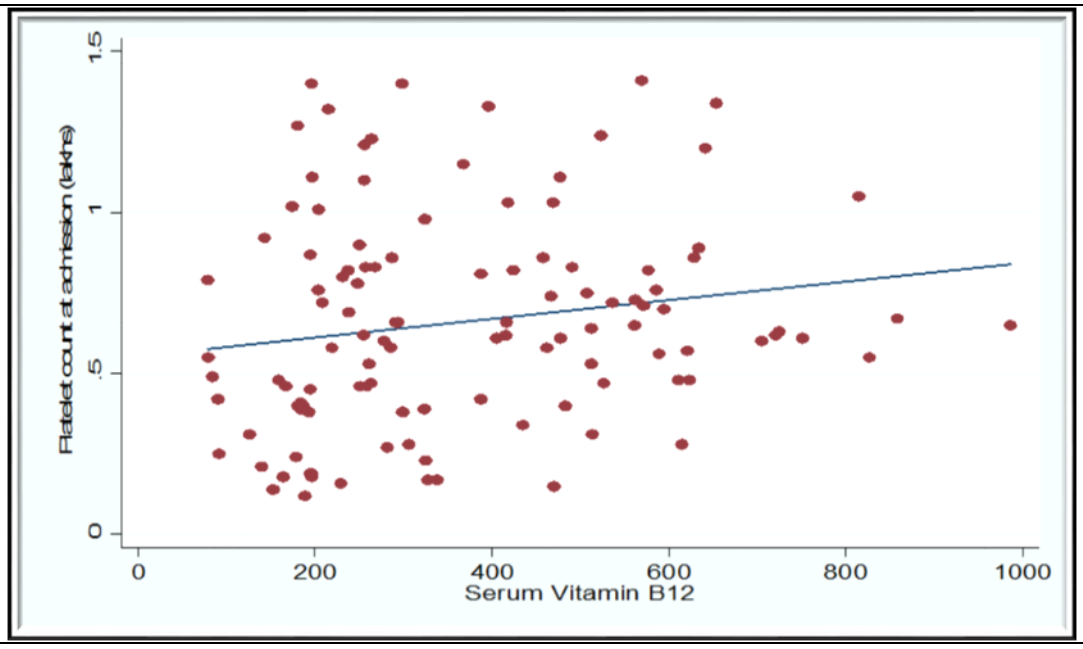


Graph 2

Vitamin B12 levels	Duration of hospital stay (Days)				Mean hospital stay (Days)
	<2	2-4	5-6	>6	
<100pg/L	0	0	3	2	6.2
101-200pg/L	2	8	6	7	5
201-300pg/L	8	11	7	3	3.8
>300pg/L	17	28	4	7	3.5
Total	27	47	20	19	
Chi square p value=0.005 (Significant)					

Table 1



Graph 3: Correlation of platelet count at admission and vitamin B12 level

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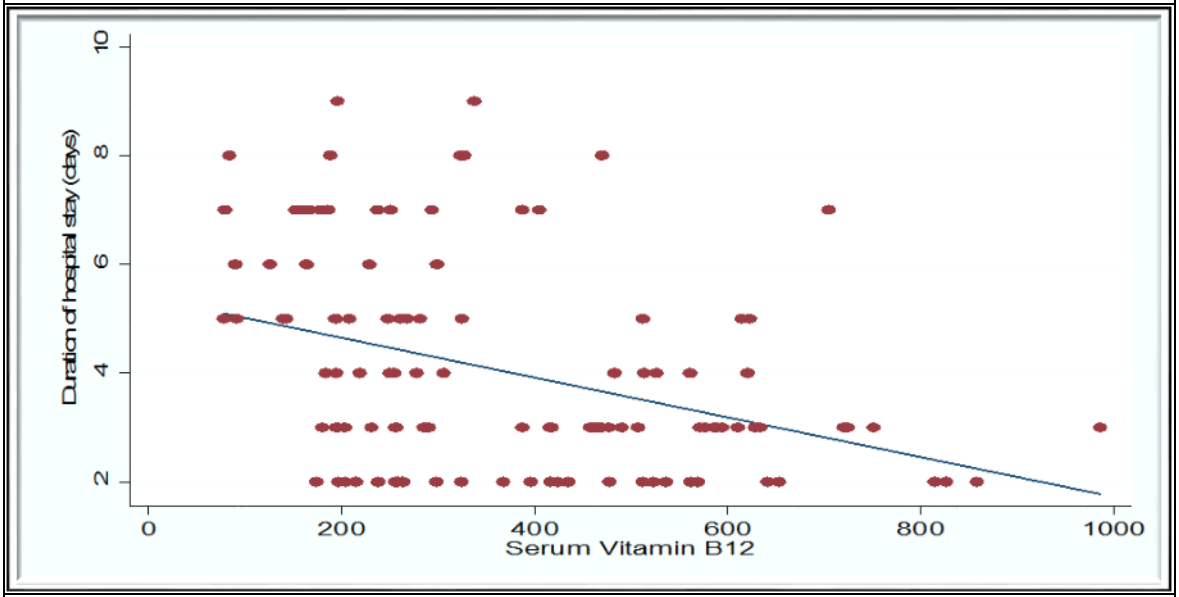

Graph 4: Correlation of duration of hospital stay and vitamin B12 level

Discussion

Often common reason for admission in patients with acute febrile illness is thrombocytopenia and risks associated with thrombocytopenia. This study was conducted with the presumption that there may be other factors contributing for severity of thrombocytopenia and recovery during acute febrile illness. Sandeep Tak et al study reports vitamin B12 deficiency may be a contributing factor to development of severe thrombocytopenia in dengue fever, particularly in Indian population.[9] Since Vitamin B12 deficiency is common in Indian population, we started this study to test the hypothesis that vitamin B12 level may have correlation with severity of thrombocytopenia and duration of hospital stay in acute febrile illness.

In the present study, nearly half of the patients (46.9%) had moderate thrombocytopenia, 26.6% patients had severe thrombocytopenia, 17.7% patients had mild thrombocytopenia and only 8.9% had very severe thrombocytopenia at admission. In Gondhali et al study, 78% cases had platelet count of >50,000/ µl platelet count at admission, 15% cases had severe thrombocytopenia and 7% cases had very severe thrombocytopenia at admission.[10] In Nair et al study, 73.4% cases had more than 50,000/ µl platelet count at admission, 25,6% cases had severe thrombocytopenia and 17.4% had very severe thrombocytopenia at admission.[11] In Suneetha et al study 46,6% patients had moderate, 26.6% patients had severe, 15.3% patients had mild and 11.3% patients had very severe thrombocytopenia at the time of presentation.[12]

In the present study, undetermined fever is the commonest cause of febrile thrombocytopenia accounting for 44(38.9%) patients. It is followed by Dengue fever in 38(33.6%) patients., and pneumonia in 15(13.3%) patients, because of seasonal, regional variations and COVID-19 pandemic. Dengue was the leading cause of febrile thrombocytopenia in Gondhali et al study and Katiyar V et al study accounting for 56% and 58.7% cases respectively.[10,5] In Suneetha et al study undetermined with 61.4% cases, was the leading cause of febrile thrombocytopenia , followed by dengue in 20% cases.[12]

In present study, among 25 vegetarians, 15 patients(60%) were vitamin B12 deficient, and among 88 non-vegetarian/mixed diet patients, 13 were vitamin B12 deficient. Thus n present study, prevalence of vitamin B12 deficiency is 24.7%. In Refsum et al study[13], prevalence of vitamin B12 deficiency is 46%, attributed to large vegetarian diet subjects and In Shobha et al study[14], prevalence of vitamin B12 deficiency is 16%, attributed to urban study subjects and

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35% of study population had multivitamin supplements.
In the present study, there was a positive correlation between serum vitamin B12 levels and platelet count severity at the admission with Pearson Correlation Coefficient of 0.174 and p-value of 0.065. Patients with vitamin B12 deficiency had low platelet count at admission, however further studies with large population required to justify the statistical significance. And in the present study, there was an inverse correlation between vitamin B12 levels and duration of hospital stay with Pearson Correlation Coefficient 0f -0.375 and p-value of <0.001. Patients with vitamin B12 deficiency had prolonged duration of the hospital stay.
In the present study, the proportion of patients requiring RDP transfusion was less in vitamin B12 sufficient patients. And there was no linear correlation between vitamin B12 levels and mortality in patients with febrile thrombocytopenia.
There are no published studies measuring these parameters against vitamin B12 level so we cannot compare with other studies.

Conclusion

Vitamin B12 deficiency may be a contributing factor to development of severe thrombocytopenia in patients of acute febrile illness with thrombocytopenia. Patients with low Vitamin B12 levels had presented with more severe thrombocytopenia, however further studies with larger population is required for confirmation. Patients with low vitamin B12 levels had prolonged hospital stay and required more number of RDP transfusion.

Limitations

This study included small sample size and conducted in a single tertiary health centre. This study included only the hospitalized patients of febrile thrombocytopenia. Further multicentre studies with large population are required for the confirmation of the findings.

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