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Evaluation of Clinical Significance of Vitamin B12 Status in Patients Admitted with Acute Febrile Illness Thrombocytopenia at Tertiary Care Hospital

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1. Abstract

1.1. Background: Thrombocytopenia is one of the most important hematological manifestations of many infections which may present with pyrexia. Vitamin B12 deficiency is highly prevalent nutritional deficiency in India and it may also be associated with low levels of platelets. This study was planned to evaluate clinical significance of vitamin B12 status in patient admitted with acute febrile illness and thrombocytopenia.

1.2. Method: Present prospective cross-sectional study was conducted on 400 consecutive patients of fever with thrombocytopenia admitted during 1st May 2022 to 31st October 2022. All patients were evaluated as per proforma including detail clinical history and physical examination. Vitamin b12 assay done in all cases by immunoassay method using unicel dxI 800 machine (Beckman Coulter). Other laboratory evaluation including CBC, RFT, LFT, blood sugar, LDH, Rapid diagnostic test for malaria, PBF for MP, test for dengue, HBsAg, Anti HCV, HIV, PBF detail, Blood culture, D–dimer, test for Scrub typhus and leptospirosis, Ultrasonography and chest X-Ray was also done in all the cases. Other investigations were done as per requirement. All patients were treated as per guidelines and followed-up during hospitalization.

1.3. Results: The mean level of vitamin B12 in our cases was 215.27±145.45pg/ml which is lower than normal range, overall low level of vitamin B12 was found in 80.5% of the cases. Prevalence of vitamin B12 deficiency was more in age group ≤20 years (82.54%) and >60 years (85%). Low levels of vitamin B12 were associated with higher MCV ($p<0.00001$) and high MPV ($p<0.02$). Lower level of Vitamin B12 were also corelated with longer duration of illness ($p<0.03$) and degree of thrombocytopenia ($p<0.02$).

1.4. Conclusion: Vitamin B12 deficiency is highly prevalent in cases of pyrexia with thrombocytopenia and it is associated with more severe thrombocytopenia, high MCV, high MPV and longer duration of illness. Vitamin B12 deficiency is found to be more prevalent in age group <20years and elderly >60years of age. Early recognition of vitamin B12 deficiency and supplementation of vitamin B12 may be helpful in reducing morbidity and mortality in such cases.

2. Introduction

Acute febrile illness with thrombocytopenia is one of the most important reasons for outdoor patient visit and hospitalization specially in tropical countries like India. It is caused by infections of varying types (viral, parasitic, bacterial) commonly like dengue, malaria, leptospirosis, scrub typhus, HIV, miliary tuberculosis etc [1-3]. Thrombocytopenia is defined as a platelet count below the lower limit of normal range (<1,50,000/μL). Thrombocytopenia associated with acute febrile illness may be due to decreased production, increased destruction (immunogenic and non- immunogenic causes) and increased sequestration by the spleen. Patients of fever with thrombocytopenia can initially present simply with fever but later on in due course of time it may lead to adverse unpredictable outcomes including death.

Vitamin B12 (cobalamin) is a water-soluble vitamin containing cobalt, it is essential for maintaining the health of all cells because it is needed for production of DNA and RNA.4 Vitamin B12 is especially important in maintaining the health of the body's nerve and blood cells. Deficiency of vitamin B12 can lead to serious complications in hematologic and neurologic systems [5]. The incidence of thrombocytopenia in symptomatic B12 deficiency is reported to be approximately 10%.6 Moreover, vitamin B12 can suppress systemic inflammation by modulating certain cytokines like interleukin [6], growth factors and other substrates with anti-inflammatory properties under normal physiological conditions [7]. Vitamin B12 can be considered an endogenous negative regulator of nuclear transcription factor-jB (NFjB) through the regulation of nitric oxide, which plays a key role in regulating the immune response to infection [8]. Vitamin B12 may also play a direct role in immune defence and inflammation through a bacteriostatic function of TCS, which is capable of modulating the inflammatory response. In addition, vitamin B12 is recognized to modulate the ecology of the gut microbiota [9]. Therefore, this study was planned to evaluate clinical significance of vitamin B12 status in patients admitted for acute febrile illness with thrombocytopenia.

3. Materials and Methods

This prospective cross-sectional study was carried out on 400 consecutive cases of acute febrile illness admitted in the Department of Medicine, Sardar Patel Medical College and associated group of Hospitals, Bikaner during 01st May 2022 to 31st October 2022 to evaluate vitamin B12. Ethics committee approval was taken before start of the study, all participating subjects were explained about the study and informed consent was taken. Inclusion Criteria: 1. Age more than 15 years. 2. Patient presented with fever and thrombocytopenia. 3. Patient giving consent. Exclusion Criteria: 1. Patient with thrombocytopenia without fever. 2. Patients with known case of thrombocytopenia like ITP, Chronic Liver Disease, Hematological disorders etc. 3. Drug induced thrombocytopenia. 4. Patient not giving consent. All patients were evaluated as per proforma including detail clinical history and physical examination. Laboratory evaluation included CBC, RFT, LFT, blood sugar, LDH, Rapid diagnostic test for malaria, PBF for MP, test for dengue, HBsAg, Anti HCV, HIV, PBF detail, Blood culture, D–dimer, test for Scrub typhus and leptospirosis, Ultrasonography and chest X-Ray was also done in all the cases. Other investigations were done as per requirement.

Vitamin B12 assay were done in all the cases by immunoassay method using unicel dxI 800 machine (Beckman Coulter). Vitamin B12 deficiency was classified according to vitamin B12 levels as per following criteria [10]

1) Deficient: Vitamin B12 level < 201 pg/ml

2) Insufficient: Vitamin B12 level 201-300pg/ml

3) Sufficient: Vitamin B12 level >300 pg/ml

In our study low status of vitamin B12 (Hypovitaminosis B12) means levels ≤300pg/ml.

Complete Blood Count was carried out using Mindray 6-part Cell counter. Thrombocytopenia was defined as total platelet count <1.5lac/cu mm and severity were graded as per NCI - CTCAE grading [11] Mild (<1,50,000-75,000/mm3), Moderate (<75,000-50,000/mm3), Severe <50,000-25,000/mm3 and Life threatening (<25,000/mm3). All the patients were treated as per guidelines. All patients were followed-up till discharge.

3.1. Statistical Analysis

Statistical analysis was done using Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Chi-square test was done for qualitative variables and Student t-test was used for quantitative variables. Pearson's Correlation test was done to evaluate correlation between B12 level with MCV and Platelet count and Multiple Linear Regression Analysis was done to predict effect of vitamin B12 in relation to various laboratory and clinical variables. $p<0.05$ was considered as statistically significant.

4. Result

Out of 400 patients 227 (56.75%) were males (age ranging 15-87 years, mean 35.46 ±15.63) and 173 (43.25%) were females (age ranging 15-92 years, mean 39.75 ± 17.36). Maximum number of patients 171(42.75%) were in age group of 15-30 years. On etiological differential diagnosis Dengue fever was found to be the commonest cause in our study (118, 29.5%) followed by Malaria (15%; 60 cases, 59 vivax and one falciparum), 3 patients (0.75%) were diagnosed with COVID-19 infection and one each HIV and Hepatitis B (0.25%) while in 54.25% of the cases (No=217) definite etiological diagnosis could not be ascertained.

Vitamin B12 status in relation to different epidemiological parameters are shown in Table 1. Overall mean level of B12 in our cases was 215.27±145.45. We found B12 deficiency in 63% of the cases and insufficiency in 17.5%, thus low status of vitamin B12 was observed in a total of 80.5% of the cases (Figure 1). Maximum number of cases with B12 deficiency and low status were observed in the age group >50 years (84.34%) followed by 15-30 years (83.05%) ($p<0.05$). Vitamin B12 status was found low in most of the patients irrespective of gender ($p>0.978$), residence urban or rural ($p>0.680$), comorbidities ($p>0.836$) and etiology ($p=0.\ 0.891$).

Table 2 shows Vitamin B12 status in relation to different Laboratory parameters. Mean value of vitamin B12 was found to be significantly corelated with anemia in female patients ($p<0.01$), MCV ($p<0.00001$), MPV ($p<0.02$) and SGPT (<0.05). Pearson correlation coefficient analysis indicated that there was a significant negative relationship between MCV and B12 LEVEL, ($r(398) = .259$, $p < .001$) (Figure 2). Abnormal haematological parameters and liver

function test were significantly corelated with low status of vitamin B12 while we do not find any corelation with renal function test. Results of the multiple linear regression indicated that there was a very strong collective significant effect between the MCV, MPV, PLATELET COUNT, TLC, SGPT, SGOT, Blood Urea, Serum Creatinine, LDH, and Vitamin B12, ($F(4, 396) = 6443.86$, $p < .001$, $R2 = 0.98$, $R2adj = 0.98$). The individual predictors were examined further and indicated that MCV ($t = 2.525$, $p = .012$) and MPV ($t = 3.005$, $p = .003$) and Platelet count ($t = 2.224$, $p = .027$) were significant predictors.

Table 3 shows Vitamin B12 status in relation to different clinical parameters. Low status of B12 was associated with longer duration of illness at the time of hospitalization ($p<0.03$). Severity of the thrombocytopenia was also significantly corelated with hypovitaminosis B12 ($p<0.02$), >81% of the patients with platelet count <50000 were having low level of B12. Pearson correlation coefficient analysis indicated that there is a significant positive relationship between Platelet count and Vitamin B12 level, ($r(398) = .101$, $p = .043$) (Figure 3). All the patients with bleeding manifestations were having low level of B12 and >76% of them were having deficiency of B12. We do not find any statistically significant difference of vitamin B12 level with duration of hospital stay and requirement for platelet transfusion.

Results of the multiple linear regression indicated that there was a very strong collective significant effect between the Duration, Stay, Age, Gender, Bleeding Manifestation, RDP, Etiology, and Vitamin B12, ($F(5, 395) = 3971.63$, $p < .001$, $R2 = 0.98$, $R2adj = 0.98$). The individual predictors were examined further and indicated that Duration ($t = 6.332$, $p < .001$) and Stay ($t = 11.723$, $p < .001$) and Age ($t = 7.431$, $p < .001$) and Gender ($t = 2.283$, $p = .023$) were significant predictors.

Table 1: Vitamin B12 status in relation to different epidemiological parameters

Parameter	No of cases (%)	Vitamin B12 status					p-value
		≤200	201-≤300	>300	Low status ≤300	Mean±SD	
B12 Status	400 (100)	252(63.00)	70(17.50)	78(19.50)	322(80.50)	215.27±145.45	
AGE							
15-30	171(42.75)	115(67.25)	27(15.78)	29(16.95)	142(83.05)	201.35±112.12	p<0.001
31-40	88(21.75)	45(51.14)	17(19.32)	26(29.55)	62(70.45)	257.01±190.16	
41-50	58(14.0)	39(67.24)	9(15.52)	10(17.24)	48(82.76)	206.25±149.65	
51-60	43(11.25)	29(67.44)	7(16.28)	7(16.28)	36(83.72)	198.56±144.44	
>60	40(10.25)	24(60.00)	10(25.00)	6(15.00)	34(85.00)	216.43±134.90	
Gender							
Male	227(56.75)	142(62.56)	42(18.50)	43(18.94)	184(81.06)	217.28±145.45	p>0.978
Female	173(43.25)	110(63.58)	28(16.18)	35(20.23)	138(79.77)	212.62±160.22	
Residence							
Urban	186(46.5)	121(65.05)	30(16.12)	35(18.82)	151(81.18)	212.82±144.54	p>0.680
Rural	214(53.5)	133(62.14)	43(20.09)	38(17.76)	176(82.24)	211.68±143.63	
Co-Morbidities							
DM	28(7)	16(57.14)	8(28.57)	4(14.29)	24(85.71)	210.06±142.31	p>0.836
HT	38(9.5)	19(50.00)	12(31.58)	7(18.42)	31(81.58)	202.81±134.40	
COPD	8(2)	6(75.00)	1(12.50)	1(37.50)	7(87.50)	210.75±149.24	
NO	337((84.5)	219(64.99)	50(14.84)	68(17.33)	269(79.82)	214.63±145.59	
ETIOLOGY							
Dengue	118(29.5)	75(63.56)	18(15.25)	25(21.19)	93(78.81)	201.78±110.34	p>0.891
Malaria	60(15)	42(70.00)	8(13.33)	10(16.67)	50(83.33)	202.35±158.91	
Covid	3(0.75)	2(66.67)	1(33.33)	0(0.00)	3(100.00)	193.00±26.91	
Undiagnosed	219(54.75)	133(60.73)	43(19.63)	43(19.63)	176(80.37)	220.56±153.55	

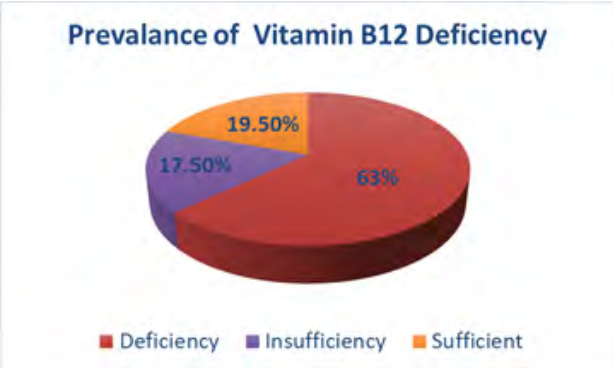

Figure 1: Showing prevalence of Vitamin B12 Deficiency and Insufficiency in Acute febrile illness with thrombocytopenia

Table 2: Vitamin B12 status in relation to different Laboratory parameters

Parameter	No of cases (%)	Vitamin B12 status					p
		≤200	201-≤300	>300	Low status ≤300	Mean±SD	
Anemia							
Yes (male)	146(64.31)	97(66.43)	30(20.54)	19(13.01)	127(86.98)	211.51±142.02	p<0.07
No (male)	81(35.69)	46(56.79)	15(18.51)	20(24.70)	61(75.30)	211.32±142.88	
Yes(female)	100(57.80)	62(62.00)	15(15.00)	23(23.00)	77(77.00)	211.71±142.62	p<0.01
No(female)	73(42.20)	48(65.75)	13(17.80)	12(16.44)	61(83.56)	209.59±141.40	
Total leucocyte count							
<4000	209(52.25)	129(61.72)	39(18.66)	41(19.62)	168(80.38)	212.78±144.72	p<0.07
4000-11000	167(41.75)	110(66.76)	28(65.86)	29(17.37)	138(82.63)	211.35±142.31	
>11000	24(6.00)	15(62.50)	6(25.00)	3(12.5)	21(87.5)	207.00±135.86	
MCV							
<80	105(26.25)	38(36.19)	32(30.48)	35(33.33)	70(66.67)	280.8±163.69	p< 0.00001
80-100	178(44.5)	128(71.91)	23(12.92)	27(15.17)	151(84.83)	199.06±137.10	
>100	117(29.25)	88(75.21)	18(15.38)	11(9.40)	106(90.60)	172.73±114.27	
MPV							
<8	93(23.25)	58(62.36)	17(18.27)	18(19.35)	75(80.65)	212.00±143.05	p<0.02
15-Aug	281(70.25)	180(64.05)	52(18.5)	49(17.43)	232(82.57)	214.21±145.53	
>15	26(6.5)	14(53.8)	1(3.8)	11(42.3)	15(57.7)	209.12±150.21	
RFT Blood urea							
≤45	324(81.00)	201(62.03)	63(19.44)	78(24.07)	246(75.93)	212.82±144.54	p>0.1
>45	76(19.00)	52(68.42)	10(13.15)	14(18.42)	62(81.58)	211.68±143.63	
Serum creatinine							
≤1.6	363(90.75)	230(63.36)	69(19.00)	64(17.63)	299(82.37)	212.82±144.54	P<0.8
>1.6	37(9.25)	23(62.16)	4(10.81)	10(27.03)	27(72.97)	207.97±136.63	
SGOT							
≤40	70(17.50)	52(74.2)	7(1.00)	11(15.72)	59(84.28)	212.46±143.16	P<0.07
>40	330(82.50)	200(60.6)	63(19.09)	67(20.31)	263(79.69)	214.63±145.59	
SGPT							
≤35	85(21.25)	62(72.94)	8(09.41)	15(17.65)	70(82.35)	212.86±143.20	P<0.05
>35	315(78.75)	190(60.32)	62(19.68)	63(20.00)	252(80.00)	214.63±145.60	
LDH							
≤420	236(59.00)	150(63.56)	39(16.53)	47(19.92)	189(80.08)	213.28±143.27	p>0.67
>420	164(41.00)	102(62.20)	31(18.90)	31(18.90)	133(81.10)	212.51±145.28	

Parameter	Value
Pearson correlation coefficient (r)	**-0.2588**
P-value	1.52E-07
Covariance	-424.8069
Sample size (n)	400
Statistic	-5.3457

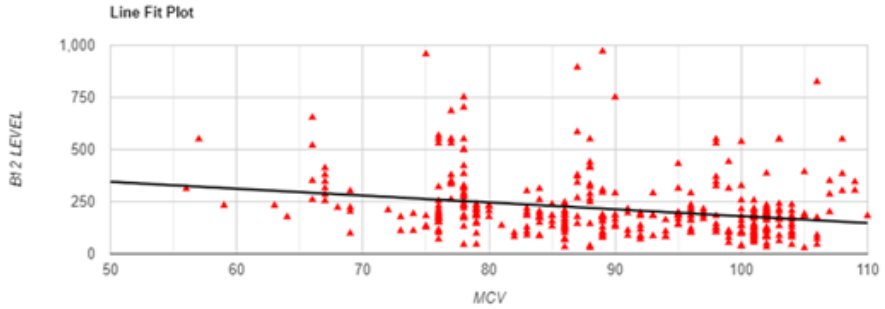

Figure 2: Results of the pearson correlation indicated that there is a significant negative relationship between MCV and B12 LEVEL, (r(398) = .259, p < .001).

Table 3: Vitamin B12 status in relation to different clinical parameters

Parameter	No of cases (%)	Vitamin B12 status					p
		≤200	201-≤300	>300	Low status ≤300	Mean±SD	
Duration of Illness (days)							
5-Jan	282(70.5)	166(62.41)	50(17.73)	66(19.86)	226(80.14)	215.27±145.45	p<0.03
10-Jun	114(28.5)	83(64.03)	19(16.67)	12(19.30)	92(80.70)	212.08±143.47	
>10	4(1)	3(75.00)	1(25.00)	0(0)	4(100.00)	214.68±152.36	
Bleeding manifestation							
Yes	17(4.25)	13(76.47)	4(23.52)	0(0)	17(100)	198.74±130.01	p>0.22
No	383(95.75)	241(62.92)	69(18.01)	73(19.07)	310(80.93)	212.82±144.54	
Severity of thrombocytopenia							
Mild	76(19)	40(52.63)	18(23.68)	18(23.68)	58(76.32)	198.99±114.19	p<0.02
Moderate	87(21.75)	62(71.26)	10(11.49)	15(17.24)	72(82.76)	227.75±137.01	
Severe	180(45)	121(67.22)	29(16.11)	30(16.67)	150(83.33)	220.44±155.54	
Life threatening	57(14.25)	29(50.88)	13(22.81)	15(26.32)	42(73.68)	204.65±162.41	
Duration of hospital stay							
<3	10(2.5)	6(60.00)	0(0.00)	4(40.00)	6(60.00)	212.32±142.24	p>0.5
5-Mar	370(92.50)	234(63.24)	65(17.57)	71(19.19)	299(80.81)	214.62±145.59	
>5	20(5)	12(60.00)	5(25.00)	3(15.00)	17(85.00)	214.79±145.74	
Need for Platelet transfusion							
Yes	42(10.5)	28(66.67)	4(9.52)	10(23.81)	32(76.19)	211.32±142.88	p>0.9
No	358(89.5)	224(62.56)	66(18.43)	68(19.00)	290(81.00)	212.82±144.54	

Parameter	Value
Pearson correlation coefficient (r)	**0.1011**
P-value	0.0433
Covariance	439903.2268
Sample size (n)	400
Statistic	2.0273

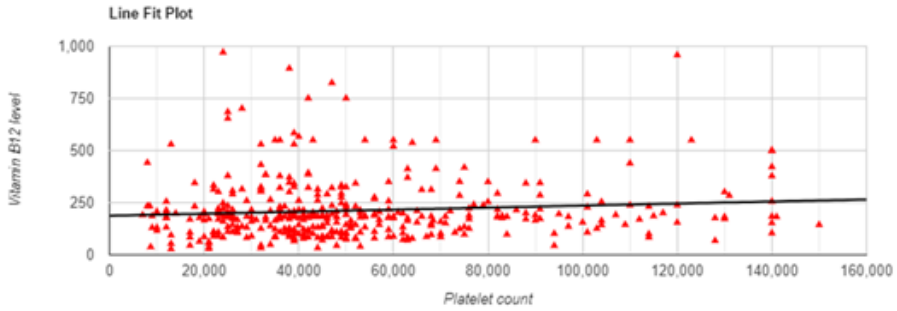

Figure 3: Results of the pearson correlation indicated that there is a significant positive relationship between Platelet count and Vitamin B12 level, (r(398) = .101, p = .043).

5. Discussion

This study was carried out in the Department of Medicine, Sardar Patel Medical College & Associate group of hospitals, Bikaner to evaluate status of Vitamin B12 level and its clinical correlation in patients admitted with acute febrile thrombocytopenia.

We observed high prevalence of vitamin B12 deficiency (63%) in our cases and overall hypovitaminosis B12 was found in 80.5% of the cases. Vitamin B12 deficiency is common in India. Singla et al (2019) reported overall prevalence of 47% in North India [12]. Yajnik et al (2006) found low level vitamin B12 in 67% of cases in Indian men particularly in vegetarian and urban middle class resident [13]. High prevalence of hypovitaminosis B12 in our cases may be because of infections (like dengue, malaria and others causing catabolic state in the body, highly prevalent vegetarian food habit etc. Sandeep Tak et al. (2018) also found lower level of vitamin B12 in patients of dengue fever associated with lower platelet count [14]. Paliwal et al (2022) concluded that Vitamin B12 deficiency may be a contributing factor to the development of severe thrombocytopenia in dengue fever, particularly in the Indian population. Vitamin B12 deficiency may prolong the hospital stay and increase the platelet recovery time [15]. Kansara and sharma (2022) found B12 deficiency was more commonly associated with thrombocytopenia in dengue than malria [16]. Mangukiya et al (2011) found low level of vitamin B12 in 70% cases in patient attending general hospital in Gujrat [17].

We found high prevalence of vitamin B12 deficiency in the age group of <20years (82.5%) and >60 years (85%). Verma (2017) did study on school going children age ranging 11-18 years and found prevalence of vitamin B12 deficiency in 72.7% adolescent [18]. Parmar et al (2015) observed that serum vitamin B12 level of elderly patients (> 60 years) was significantly lower as compared to other age group (p< 0.005) [19].

In the present study we found that patients with vitamin B12 deficiency were having lower mean platelet count (51757.50±30486.26) as compared to patients with sufficient level of vitamin B12 (>301pg/ml). Panchabhai et al (2016) reported a case of thrombocytopenia in a patient with severe vitamin B12 deficiency which recovered after Vitamin B12 replacement therapy [20]. We found vitamin B12 levels were negatively corelated with MCV. High MCV (macrocytosis; MCV>100) was present in 117 of the cases out of which 90.6% were having low level of B12. Ankar et al found that among patients with clinical macrocytosis (defined as an MCV >100), 18% - 20% were having to B12 deficiency [10].

We observed that patients with longer duration of illness were having lower level of vitamin B12. Tak et al (2018) reported that lower level of vitamin B12 were associated with lower level of platelet count, longer duration of illness and longer duration of hospital stay in dengue fever [14].

6. Conclusion

We found vitamin B12 deficiency is highly prevalent in cases of pyrexia with thrombocytopenia and it is associated with longer duration of illness, more severe thrombocytopenia and longer duration of hospital stay. Vitamin B12 deficiency is found to be more prevalent in age group <20years and elderly >60years of age. Early recognition of vitamin B12 deficiency and supplementation of vitamin B12 may be helpful in reducing morbidity and mortality in such cases.

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