

Study to assess the etiology of vitamin B12 deficiency in patients of north Karnataka

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Abstract

Background: Vitamin B12 deficiency related anemia is a common form of anemia noted in our patients. Due to rising clinical awareness, the deficiency is recognized with increasing frequency. B12 deficiency is also known to have varied clinical spectrum than previously recognized. Prognosis of B12 deficiency is variable and its outcome may vary from complete recovery to permanent neurological deficits. **Aims and objectives:** To assess the etiology of Vitamin B12 deficiency in patients with B12 deficiency related anemia. **Methods:** 75 patients diagnosed with vitamin B12 deficiency were assessed to study the etiology. Data collected was analyzed and different levels of vitamin B12 and different age groups were correlated with sex, diet pattern, etiology, anti intrinsic factor antibody (AIFA) and levels of B12 deficiency. **Results:** Of the 75 patients analyzed, 44 (58.7%) were males and 31(41.3%) were females. The mean age was 35.8 yr with majority of patients (33.3%) in the age group 21-30 years. 57 (76%) patients were strict vegetarians while 18 (25 %) were on mixed diet. Patients presented with general weakness (66.7%), severe anorexia (60%), dyspnoea on exertion (40%), giddiness, tingling and numbness (33.3%), jaundice (20%), and ataxia (9.3%). Mean Hb was 6.14 g% (range 1.7-11.2g%) with MCV of 111.37fL (64.9-134fL). The mean serum vitamin B12 level was 125.94 pg/ml, range 30-120 pg/ml. Inadequate dietary intake (nutrition) was the most common etiology seen in 48 patients (64%), followed by alcohol in 14 (18.7%) and pernicious anemia in 9 (12%) patients. **Conclusion:** We observed that vitamin B12 deficiency is commonly seen in our region, which might be due to insufficient dietary intake of vitamin B12 and can be described as a treatable disease with good short and long term outcomes. Clinical signs and symptoms, etiology, in this study were similar to those of other studies.

Key Words: Vitamin B12 deficiency; Etiology; Pernicious anemia.

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jaundice (including recurrent jaundice) and/ or important neurological manifestations such as paraesthesias, loss of balance, difficulty in walking, mental changes, Lhermitte's symptoms and impotence. Some of the dietary sources of vitamin B12 include dairy products, eggs, liver and kidneys of animals. Deficiency of vitamin B12 occurs due to poor intake and/or malabsorption of dietary cobalamin. A review of previous studies for the study of etiology of vitamin B12 deficiency, found limited literature in patients from this part of the country. Hence, we decided to investigate and study the various etiologies for vitamin B12 deficiency in our patients.

INTRODUCTION

Vitamin B12 (cobalamin) deficiency is a common condition seen both in outpatients as well as in inpatients. Previous studies have shown prevalence of B12 deficiency ranging between 3-40% in adult population^{1,2}. The manifestations vary from being completely asymptomatic to wide range of symptoms due to anemia,

MATERIAL and METHODS

This is a prospective study done over a period of 2 years from December 2015 to December 2017. Approval from Institutional Ethics Committee (IEC) for the research study was obtained. A total of 75 patients with vitamin B12 deficiency both from OPD and IPD from 3 different

tertiary care hospitals, which render services to 3-4 districts of North Karnataka, were analyzed for the etiology of vitamin B12 deficiency. History and presenting symptoms of patients were taken in detail. Symptoms due to anemia like easy fatigability, general weakness, palpitations, giddiness, bilateral lower limbs swelling, jaundice, including first time or recurrent jaundice, and neurological symptoms such as tingling and numbness, difficulty in walking, giddiness, cognitive disturbances and any other symptoms were noted. Dietary history was taken in detail by 24 hour food recall method. Patients were examined for pallor, icterus, glossy tongue, cheilosis, cheilitis, edema, knuckle hyper pigmentation, vitiligo and a detailed neurological examination was done. Laboratory investigations included complete blood count (CBC) with red cell indices, peripheral smear study, liver function tests, LDH, TSH, serum vitamin B12 levels and anti-intrinsic factor antibody (AIFA). Serum vitamin B12 was estimated by chemiluminiscence

immunoassay. Normal serum B12 level varies between 211-911 pg/ml, deficiency is defined as levels <200 pg/ml^{3,4,5}. Pernicious anemia was said to be present when AIFA were elevated (AIFA B >1.1 units, sensitivity 50% and specificity 100%)⁶. Patients with age <15 years, obvious gastrointestinal bleeding and gastric cancer were excluded from the study.

Statistical Analysis

The results were analyzed using SPSS Version 20.0, results on continuous measurements were presented on mean±SD (min-max) and results on categorical measurements were presented in number (%). Normality of data was assessed using Shapiro-Wilk test – Mann-Whitney U-test, Chi-square test with Yate’s correction was used to find out the significant difference between the groups, Spearnans correlation was used to find out the relationship between the variables. Significance was assessed at 5%.

RESULTS

Out of 75 cases studied 44 (58.7%) were males and 31 (41.3%) were females (fig.1), with predominant patients being young adults between 21-30 years (table No.1).

Table 1: Age wise distribution of Cases

Age group (years)	Frequency (n)	%
≤ 20	15	20.0
21-30	25	33.3
31-40	11	14.7
41-50	09	12.0
>50	15	20.0
Total	75	100.0

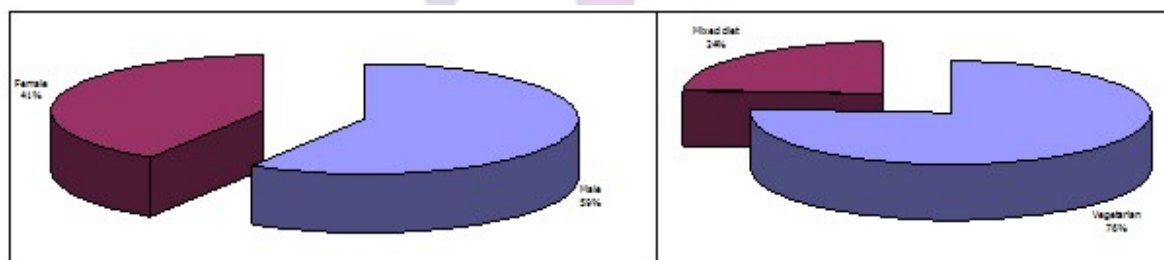


Figure 1: Gender Distribution of Cases

Figure 2: Dietary Pattern wise distribution of cases

In figure 1, Majority of patients (n=57, 76.0%) were strict vegetarians as compared to mixed diet (n=18, 25%) (fig.2). Generalized weakness (n=50, 66.7%) was the commonest symptom followed by severe anorexia (n=45,60.0%), dyspnoea on exertion (DOE) (n=30,40.0%), giddiness, tingling and numbness of extremities (n=25, 33.3%) and jaundice (n=15 20.0%). 7 patients (9.3%) had ataxia (table No. 2).

Table 2: Clinical Presentation

Symptoms	Frequency (n)	%
General weakness	50	66.7
Anorexia	45	60.0
DOE	30	40.0
Giddiness, tingling and numbness of extremities	25	33.3
Jaundice	15	20.0
Ataxia	7	9.3

Pallor was seen in all patients (n=75, 100%), followed by knuckle hyperpigmentation (n=33, 44.0%) (figure 3), hepatomegaly (n=28, 37.3%), jaundice (n=17,22.7%) and splenomegaly (n = 15, 20.0%). 7 patients (9.3%) had Romberg's sign positive (table No.3).



Figure 3: Knuckle hyper pigmentation

Table 3: Clinical Signs of cases

Clinical signs	Frequency (n)	%
Pallor	75	100.0
Knuckle hyperpigmentation	33	44.0
Hepatomegaly	28	37.3
Jaundice	17	22.7
Splenomegaly	15	20.0
Romberg's sign	7	9.3

18 patients (24.0%) had significant alcohol consumption, as compared to 57 (76.0%), who were non-alcoholics or had minimal alcohol consumption (significant alcohol consumption defined as alcohol intake > or equal to 60-80g/day for 10 years or longer in men and > or equal to 20 g/day in women)⁷. The mean and SD of Hb% g was 6.14±2.18, (range 1.7-11.2), the mean and SD of MCV in fL was 111.37±13.90 (range 64.9-134). Platelets (in lakhs) were also on lower side in the study population with mean and SD as 1.29 ± 0.69, (range 0.09-3.20 lakhs). The other RBC indices are mentioned in the table No.4.

Table 4: Blood count

	Mean ± SD	Range
Hb (g%)	6.14±2.18	1.7-11.2
MCV (fL)	111.37±13.90	64.9-134
TC (in thousands)	4941.3±2099.75	1500-10000
Platelets (in lakhs)	1.29±0.69	0.09-3.20
HCT	22.26±7.2	6.5-40
MCH	33.35±2.9	27.0-39.75
MCHC	32.82±1.93	26.1-37.40

The mean and SD of serum vitamin B12 levels (in pg/ml) in the study population was 125.94 ± 56.96 (range 30-210). Values in different age groups is given in table No.5

Table 5: Serum Vitamin B12 Levels in different age groups

Age in years	Vitamin B12 level (in pg/ml)
< 20	123.7

21-30	131.9
31-40	107.0
41-50	122.4
> 50	124.6
Mean ± SD	125.94 ± 56.96

The serum vitamin B12 level between males and females, vegetarians and mixed diet population and alcoholic and non-alcoholics is shown in the table No.6, There was no statistical significance between the groups (P>0.05)

Table 6: Comparison of Vitamin B12 Levels

	Mean±SD		Man-Whitney U value	P value
	Male	Female		
Serum B12	129.88±54.25	120.35±61.07	630	0.57
	Vegetarian	Mixed diet		
Serum B12	125.41±57.05	127.64±58.29	497.50	0.85
	Alcohol	Non-alcohol		
Serum B12	129.30±54.96	124.86±58.02	487.50	0.75

The anti IF antibody was found positive in 9 patients (12%) (Figure-4).

In the study population, deficiency of vitamin B12, noted predominantly in strict vegetarians, was found to be the commonest etiology for B12 deficiency (n=48, 64.0%) due to poor nutritional intake. This was followed by deficiency seen in alcoholics (n=14, 18.7%), 9 patients (12.0%) had pernicious anemia, 3 patients (4.0%) had both nutritional deficiency as well as alcohol as their etiology for vitamin B12 deficiency. 1 (1.3%) patient was on long standing (from 7 years) metformin therapy as the etiology for B12 deficiency without evidence for any other cause (figure-5)

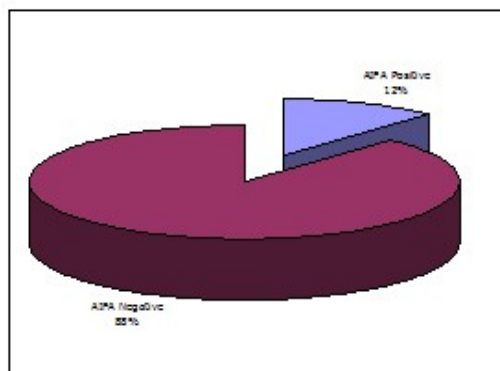


Figure 4

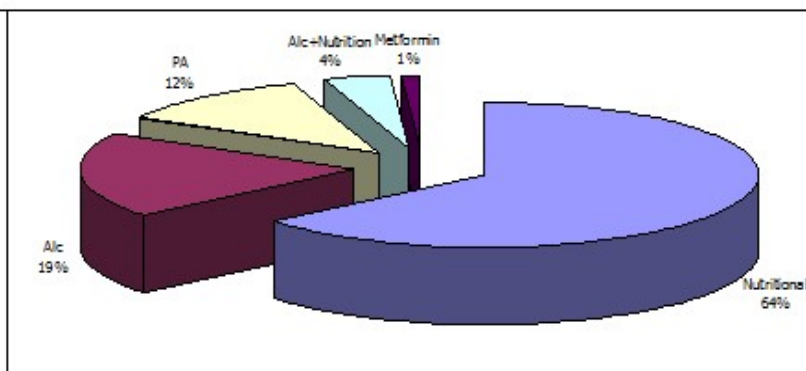


Figure 5

When S.vitamin B12 levels were compared with different etiologies of B12 deficiency, there was no statistically significant difference observed between different levels of vitamin B12 with etiology (P>0.05) (table No.7).

Table 7: Etiology of Vitamin B12 Deficiency

	Vitamin B12		Chi-square value	P-value
	Up to 100	101-210		
Nutrition	16	32	2.086	0.719
Alcohol	3	11	-	-
Pernicious anemia	5	4	-	-
Nutrition + Alcohol	0	3	-	-
Metformin	1	0	-	-
Total	25	50	-	-

When age was compared with etiology, for B12 deficiency, there was a statistically significant difference observed between different levels of age with etiology (P>0.05) with most alcoholics presenting in middle age and PA in older age group (table No.8).

Table 8: Etiology wise distribution of cases

	Age					Man-Whitney U value	P value
	≤20	21-30	31-40	41-50	≥51		
Nutrition	14	20	4	2	8	35.38	0.0035
Alcohol	0	4	5	4	1	-	-
PA	1	1	0	1	6	-	-
Nutrition+Alcohol	0	0	2	1	0	-	-
Metformin	0	0	0	1	0	-	-
Total	15	25	11	9	15	-	-

DISCUSSION

Vitamin B12 (Cobalamin) is required for reactions catalyzed by the enzymes, methionine synthase and methylmalonic acid mutase, and thus participates in methionine and succinyl Co-A synthesis. The RDA for cobalamin is 2.4mcg/day⁸. The vitamin is synthesized by micro-organisms and detected in trace amounts mostly in foods of animal origin⁵. The vitamin is relatively stable during cooking and processing. Absorption of vitamin B12 is relatively complex. Uptake in GI tract depends on intrinsic factor (IF), which is synthesized by gastric parietal cells, and is absorbed by the “cubum receptor” in the distal ileum⁹. Our study included 75 patients with vitamin B12 deficiency, majority of patients being males and in the age group of 21-30 years. Similar male preponderance was observed in other studies^{10, 11}. Symptoms due to anemia such as generalized weakness, anorexia, DOE and giddiness were the commonest presentation of our patients (66.7%), followed by symptoms due to peripheral neuropathy (33.3%) and jaundice (20%). In study by Sapte *et al* and R.Nalvi *et al*, 96.7% and 72.5% respectively had similar complaints due to B12 deficiency related anemia^{12, 13}. In the studies performed by H.Nafil *et al* (14), Khanduri V *et al*¹⁵ and S.Apte *et al*¹², the most common presenting sign was pallor (93.3%, 85% and 66.3% respectively). Similar observation was made in the present study with pallor being the most common presenting clinical sign seen in all study patients (100%). Knuckle hyperpigmentation (44%) was the second commonest presentation in our study. Other presenting signs included hepatomegaly (37.3%), icterus (22.7%) and splenomegaly (15%). Hematological findings in our study group showed severe anemia (Hb-6.4 g%±2.17), thrombocytopenia (20%) and pancytopenia (34.6%). Similarly other studies have also found significant anemia, pancytopenia and thrombocytopenia in their study subjects with vitamin B12 deficiency^{12, 14, 16}. The mean cobalamin levels in our study group was 125.94±56.58 pg/ ml, without a statistically significant difference between male and female group (p-value <0.185) and between vegetarians and mixed diet individuals (p value<0.566). We postulate that the commonest etiology for vitamin B12 deficiency is poor nutritional intake from vegetarian diet in our study

group. This could be probably because most patients in this part of the country (North Karnataka) are majority from middle-low income group and rice consumers with few population consuming mixed diet. Similar observations of poor nutritional intake as a cause for significant vitamin B12 deficiency was also made by E.Korkut *et al*¹⁷ and Surana A *et al*¹⁸ group. The second common etiology was alcohol abuse, as alcohol is shown to have direct toxic effect as well as vitamin B12 and folic acid deficiency due to poor nutrition¹⁹. In our study AIFA was found positive in 9 (12%) of patients, predominantly in patients above 50 years (6 out of 9, 66.6%), thus being third commonest cause for B12 deficiency. Pernicious anemia is the most common cause of B12 deficiency in the West²⁰. In a study from India, Aaron S *et al*¹¹, showed AIFA positive in 19 among 63 (30.15%) study population. Desai HG showed in their study that 16 patients who presented with severe vitamin B12 malabsorption had 2 patients (12.5 %) with AIFA positive and 4 patients (25%) with antiparietal cell antibody (APCA) positive (21). Various drugs such as HAART, metformin, anticonvulsant are known to cause macrocytosis¹⁹. In our study, 1 patient was on metformin therapy, without any other identifiable cause for his B12 deficiency status.

SUMMARY

In summary, the present study emphasizes that vitamin B12 deficiency is not an uncommon condition in our population. A high index of clinical suspicion is needed to diagnose this condition in patients with anemia and jaundice as well as other neurological disorders so that appropriate therapy can be started at earliest. This condition is common in both old as well as young adult population. Our study showed that poor dietary intake due to vegetarianism, followed by ethanol intake and pernicious anemia as the common causes for B12 deficiency. Finally, vitamin B12 deficiency can be described as a treatable disease with good short and long-term outcomes.

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