

A PROSPECTIVE CROSSECTIONAL STUDY OF PREVALENCE OF NEUROPSYCHIATRIC MANIFESTATIONS IN ADOLESCENTS WITH VITAMIN B12 DEFICIENCY ANAEMIA

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ABSTRACT

Background: Megaloblastic anemia is one of the common causes of anemia in adolescent population. Anemia being the most common presentation of B12 deficiency, the neuropsychiatric features are often overlooked. In India limited studies are available on vitamin B12 deficiency in adolescents. The aim of this study was to determine the prevalence of neuropsychiatric features in adolescents presenting with vitamin b12 deficiency. **Method:** A Prospective, tertiary hospital based, cross sectional open label clinicoepidemiological analysis of 100 anaemic patients of adolescent age group (excluding aplastic anaemia, hemolytic anaemia associated with jaundice and organomegaly, leukaemia, anemia of chronic inflammatory diseases, those who had received blood transfusion or haematinics in past (< 6months)) admitted in pediatric ward of tertiary care centre in Ajmer region was done. In all the cases detailed clinical history and general examination along with lab investigations were done. In all the cases vitamin B12 level was done. **Results:** Out of 100 patients 38% were found deficient with female predominance. A prominent association could be ascertained between neuropsychiatric symptoms and B12 deficiency. **Conclusion:** Deficiency of B12 is increasing among adolescents during recent years, with neuropsychiatric symptoms being common clinical features as seen in our study. B12 deficiency might present with these symptoms in absence of anemia. Supplementation through implemented nutritional programmes and education regarding diet patterns may overcome this deficiency.

Keywords: Megaloblastic Anemia, Neuropsychiatric Morbidity, Adolescents Age

INTRODUCTION

B₁₂ deficiency is one of the leading causes of megaloblastic anemia and can occur at any age. The clinical features of B12 deficiency are highly variable and may be atypical at times. Early diagnosis is important and early treatment gives better results. Although uncommonly causing megaloblastic anemia, mild deficiency is more commonly associated with neurocognitive features. Vitamin B₁₂ insufficiency has been traditionally thought to be infrequent in adolescent age, however, recent learnings advocate that this condition is more prevalent than recognized earlier.

Vitamin B₁₂ deficiency leads to myriad neurological manifestations and affects all age groups (1). Early recognition of this condition is essential, as it is reversible and preventable (2). However, a significant diagnostic delay still occurs in many cases. The association of B12 deficiency with megaloblastic anemia, GIT and central as well as peripheral neurological abnormalities have been identified in several clinical case reports/series by Combe, Addison and autopsy case reports by Flint, Fenwick, Cahn and Von Mehning since the early 19th century. Gardner and Osler in their case report described a patient with anemia who had progressive numbness in fingers, hands, forearms and difficulty in buttoning his clothes and using

tools (3). Liechtenstein described the relationship of PA and spinal cord disease but associated both to Tabes Dorsalis (4). Lichtheim and Minnich acknowledged the histologic distinction in the spinal cord between Pernicious Anemia and Tabes Dorsalis. (5)

Various clinical manifestations of vitamin B12 deficiency reported in children are:

- General
 - Weakness
 - Fatigue
 - Anorexia
 - Failure to thrive
 - Irritability
- Neurologic/psychiatric
 - Developmental delay/regression
 - Paraesthesia
 - Impaired vibratory and proprioceptive sense
 - Hypotonia
 - Seizures
 - Ataxia
 - Dementia
 - Paralysis
 - Abnormal movements
 - Memory loss
 - Personality change
 - Poor school performance
 - Depression
- Hematologic
 - Macrocytosis
 - Anemia
 - Hypersegmentation of neutrophils
 - Leukopenia
 - Thrombocytopenia
 - Pancytopenia
- GIT
 - Bleeding per rectal
 - Glossitis
 - Diarrhoea / vomiting
 - Icterus
- Other features
 - Skin hyperpigmentation
 - Systolic flow murmur

The objectives of present study were to study the clinical presentation of vitamin B12 deficiency and to detect the prevalence of neuropsychiatric manifestations in children with anemia of B12 deficiency.

METHODS

100 Cases admitted in pediatric ward of JLN Medical college Ajmer were enrolled in the study by excluding Aplastic anemia, Haemolytic anemia associated with jaundice and organomegaly, leukaemia, Anemia of chronic inflammatory diseases and those who had received blood

transfusion or haematinics in past (< 6months). In every case detailed history including Clinical, developmental, dietary and detailed clinical examination including General, neurological, haematological and abdominal were done. Written informed consent was taken from caregiver of each patient, following which blood investigations were done including complete blood count, blood indices and peripheral blood film for cellular morphology. In every case serum Vitamin B12 level was done by using automated chemiluminescent immunoassay technique.

Estimation of haemoglobin levels

Haemoglobin levels were estimated using Bekmann and Coulter LH 500 automated hematology analyzer. Diagnosis of anaemia was made when the haemoglobin (Hb) level in blood was below the lower value of the normal range as per the age and sex of the patient. Adolescents patients (age 10-18 years) visiting the OPD or admitted within the hospital, and having haemoglobin value < 12 gm/dl in those upto 14 years of age; < 13 gm/dl in males 15 years and above and < 12 gm/dl in non-pregnant females of 15 years and above as per WHO, were considered to be anaemic. (6) Complete blood count (CBC) remains a practical starting point in the laboratory evaluation and classification of B12 deficiency anemia's and consists of estimation of haemoglobin, RBC indices like, MCV (mean corpuscular volume), MCHC, MCH (mean corpuscular haemoglobin) and peripheral smear, platelets count, total leucocyte count. In every case serum B12 level was estimated by automated chemiluminescent immunoassay (Table 1).

The scholastic performance was obtained from the progress report for the period of past six months based on the grading system. Psychometric analysis was done based on GHQ (General Health Questionnaire) score and HDRS (Hamilton Depression Rating Scale-17) by paediatric psychiatrist and were graded according to the points obtained.

TABLE 1: Normal value in Adolescents

Normal values	Adolescents
Hb	13.0-16.0 gm/dl
MCV	79-98 fl
MCHC	32-36 %
MCH	25-35 pg
RDW	11.5-14.0 %
Total RBC	4.50-5.30 (x106 /µl)
Platelets	150-450 (x103/µL)
TLC	4.5-13.0 (x103/µL)
Serum Vitamin B12 level	Normal values are 200-900 (pg/mL)

Statistical analysis

The data obtained was coded and entered into Microsoft Excel Worksheet. The categorical and continuous variables were expressed as as rate, ratio, proportion and mean \pm standard deviation (SD) respectively. Categorical data was analysed using chi-square and Fisher's exact test. Continuous data was compared by independent sample t test. A p- value of <0.05 was considered as statistically significant.

RESULTS

A total of 100 adolescent children aged between 10 to 18 years were included with 62% normal serum B12 level ($>200\text{pg/dl}$) and 38% were deficient ($<200\text{pg/dl}$). In this study 42% were male and 58% were female with nonsignificant but higher incidence (68%) of B12 deficiency in females ($P=0.9833$).

In present study significant association was seen between neurological features (tremor/ataxia/sensory features) (21.05%) and Vitamin B12 deficiency ($p=0.012$) (Table- 2). Assessment of depression based on HDRS-17 showed significant association between B12 deficiency and score >7 (68.42%) as sign of mild depression ($p=0.0169$) (Table 3). In this study with regard to scholastic performance, 53% of the children had secured grade III, 32% % secured grade II and 15% children had secured grade I. The prevalence of vitamin B12 deficiency was high in children with grades III (55.26%), II (34.67%), I (8.55%) suggesting a nonsignificant but increasing frequency of vitamin B12 levels with decrease in scholastic function ($p=0.6155$) (Table 4). Further, the cognitive function was assessed using GHQ Score and no significant relation was found between B12 deficiency and low GHQ score as cognitive dysfunction ($p=0.349$) (Table 6).

Table 2: Association between B12 deficiency and neurological manifestations (Tremor/ataxia/sensory changes)

Neurological sign	B ₁₂ def (%)	B ₁₂ Normal (%)	Total	X ²	P value
Present	8(21.05%)	3(4.83%)	11		
Absent	30(78.94%)	59(95.16%)	89	6.17	0.012
Total	38	62	100		

In this study there was significant association ($p=0.012$) between B12 deficiency and neurological manifestations (21.05%) compare to normal level group (4.83%).

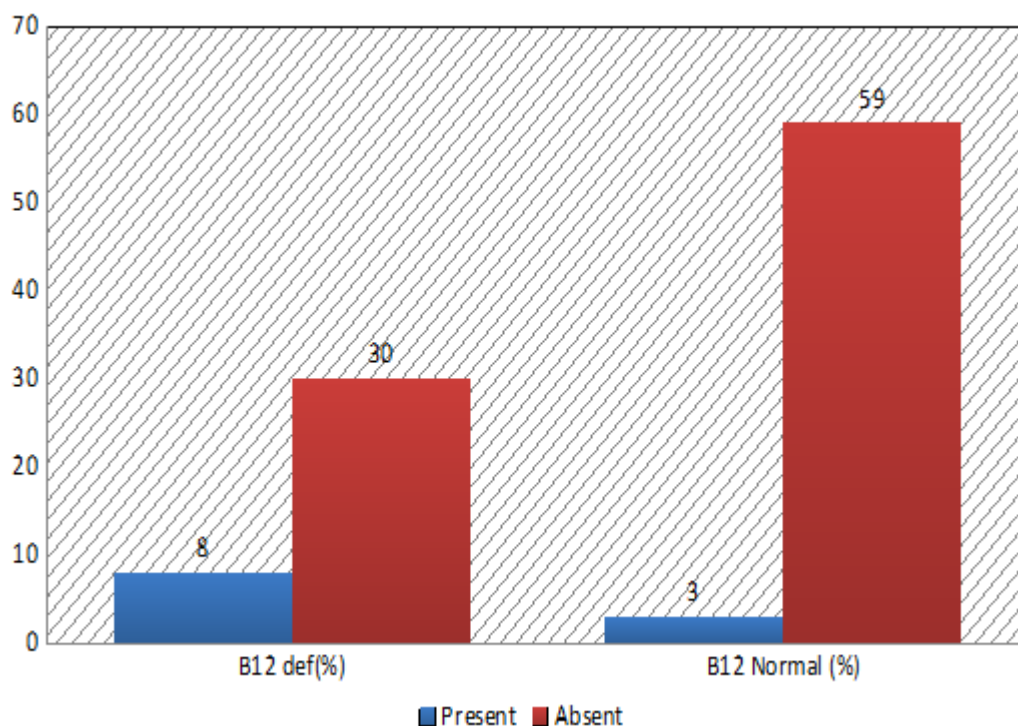


Table 3: Association between B12 deficiency and depression HDRS (Hamilton Depression Rating Scale-17)

HDRS-17	B ₁₂ def (%)	B ₁₂ Normal (%)	Total	X ²	P value
≥7	26(68.42%)	52(83.87%)	81		
<7	12(31.57%)	7(11.29%)	19	5.7	0.0169
Total	38	62	100		

In this study there was significant association (p=0.0169) between B12 deficiency and depression (68.42%) HDRS ≥ 7.

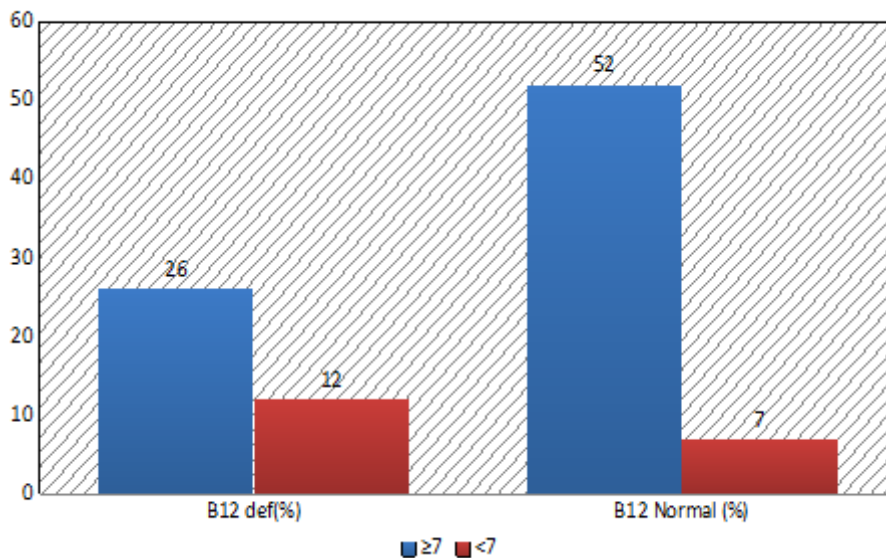


Table 4: Association between B12 deficiency and school performance

Grade	B ₁₂ def (%)	B ₁₂ Normal (%)	Total	X ²	P value
I	4(10.5%)	11(17.74%)	15		
II	13(34.21%)	19(30.64%)	32		
III	21(55.26%)	32(51.61%)	53	0.97	0.6155
Total	38	62	100		

School Performance

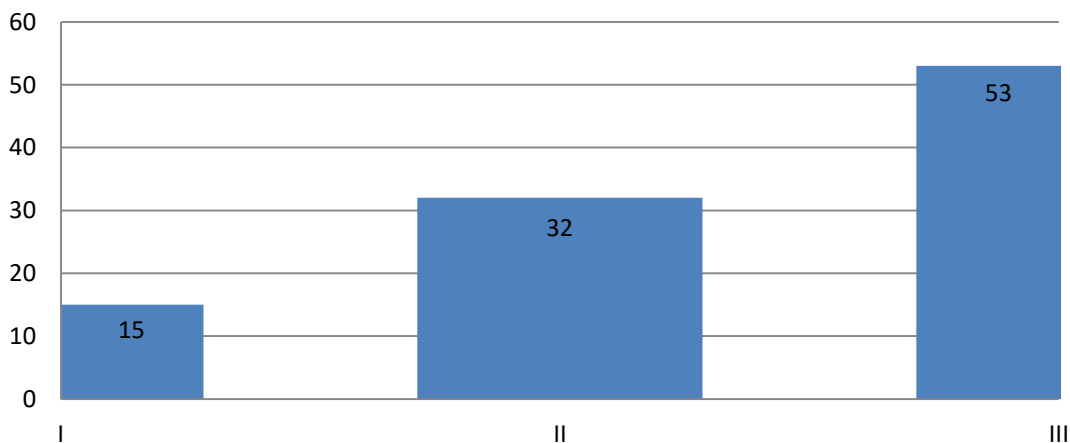


Table 5: GHQ (General Health Questionnaire)

Score	N	%
≥ 5	19	19
< 5	81	81
Total	100	100

DISCUSSION

Adolescence is a period of transition between childhood & adulthood, is second to infancy as the period of most rapid growth. During this period with inadequate & improper dietary habits, one is vulnerable to all kinds of nutritional morbidities. Bone marrow failure and demyelination of nervous tissue is a reversible manifestation of Vitamin B12 deficiency for which early diagnosis and management is important. It has to be emphasized again that neuropsychiatric symptoms, like other symptoms, can precede the development of anaemia, sometimes even with years, and that they can occur with a normal complete blood count. It is, to say the least, remarkable, that in 2019, more than 55 years after A.D.M Smith's 'Megaloblastic Madness'(7), this knowledge has been lost, and many physicians do not consider a B12 deficiency as a possible cause for symptoms, or do not want to test B12 when there is no anaemia present.

The present study was undertaken to evaluate the haematological, biochemical parameters, neurological and gastro intestinal symptoms to aid in understanding the vitamin B12 deficiency anemia in adolescent children in nutritional anemia. The main goal of our study was to determine the prevalence of neuropsychiatric features in adolescents presenting with vitamin b12 deficiency.

100 cases were enrolled in the one-year study by excluding Aplastic anemia, Haemolytic anemia associated with jaundice and organomegaly, leukaemia, Anemia of chronic inflammatory diseases and those who had received blood transfusion or haematinics in past (< 6months). In every case detailed history including clinical, developmental, dietary and detailed clinical examination including General, neurological, haematological and abdominal was done. Written informed consent was taken from caregiver of each patient, following which blood investigations were done including complete blood count, blood indices and peripheral blood film for morphology. In every case serum Vitamin B12 level was done. The scholastic performance was obtained from the progress report for the period of past six months based on the grading system.

Psychometric analysis was done using GHQ (General Health Questionnaire) score and HDRS (Hamilton Depression Rating Scale-17) by the paediatric psychiatrist and were graded as per the points secured. In present study the vitamin B12 levels were low (<200 pg/mL) in 38% of the study population as found in study done by Chandra et al.(8)

Micronutrients are essential to neurocognitive development; Deficiencies of nutrients such as vitamin B12 are more commonly associated with impairment of memory, learning ability and concentration difficulties, yet their role in educational outcomes is unclear. In this study with regard to scholastic performance, 53% of the children had secured grade III, 32% % secured grade II and 15% children had secured grade I. The prevalence of vitamin B12 was high in children with grades III (55.26%), II (34.67%), I (8.55%) suggesting a nonsignificant but increasing frequency of vitamin B12 levels with decrease in scholastic function (p=0.6155). Further, the cognitive function was assessed using GHQ Score and no significant relation was found between B12 deficiency and low GHQ score as cognitive dysfunction(p=0.349) as in study done by MM Black et al and MW Louwman et al in 2000-03. (9-10) Assessment of depression based on HDRS-17 showed significant association between B12 deficiency and score >7(68.42%) as sign of mild depression (p=0.0169) as in study by J Lindenbaum et al 1988. (12)

The neurological findings such as tremors and parasthesias were low and found only in 4 patients (4%). This was consistent with and DG Savage et al and G. Scalabrino. (13) In present study significant association was seen between neurological features (tremor/ataxia/sensory features) (21.05%) and Vitamin B12 deficiency (p=0.012).

CONCLUSION

Thus, we conclude that B12 deficiency should be suspected in atypical extra hematological presentation of adolescent anemia. The addition of vitamin B12 along with iron and folate tablets in the ongoing school health programmes which can have considerable benefits to prevent vitamin B12 deficiency thereby improving the scholastic /cognitive performance and hematological/extra

hematological manifestations. Periodic screening of adolescents may detect B12 deficiency at an early stage and need for other supplements. Education about proper dietary habits is very essential.

RECOMMENDATION

Large scale studies on the prevalence and etiology of Cobalamin deficiency in children and adolescents is needed as in recent years Cobalamin deficiency is increasing globally.

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