

Vitamin B12 deficiency in children from Northern India: Time to reconsider nutritional handicaps

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ABSTRACT

Background and Aims: Subclinical Vitamin B12 deficiency is a very common entity in the Indian subcontinent with devastating clinical and socio-economic consequences. The objective of this study was to estimate the proportion of vitamin B12 deficient children and to evaluate their clinical profile. **Setting and Design:** This prospective analytical study was conducted in a tertiary level care institute in Northern India. **Materials and Methods:** Children with clinical pallor, were included in this study. Detailed history, height, weight percentiles and characteristic features of vitamin B12 deficiency were recorded and complete blood counts, mean corpuscular volume and vitamin B12 levels were done. **Statistics:** For Qualitative data was analyzed using Pearson Chi square tests and quantitative data was analyzed using two sided independent samples t tests. **Results:** A total of 111 children were included. 64.8% (n = 72) had vitamin B12 deficiency. Lethargy (63.9%) and weight loss (62.1%), Knuckle pigmentation were common features. One-fourth of the children were on vegetarian diet. Neurological manifestations were significantly associated with fragile hair (*p* 0.056) and knuckle pigmentation (*p* 0.027). Younger children had more weight loss (*p* 0.001), knuckle pigmentation (*p* 0.019) and hypotonia (*p* 0.045). One fifth of children presented with neurological manifestations. **Conclusions:** Two-thirds of the anemic children had vitamin B12 deficiency. There was a bimodal age distribution with regard to B12 deficiency. Neurological manifestations were predominant in younger children [*<*6] and hematological abnormalities were more frequent in older children [*≥*6 years]. Estimation of vitamin B12 levels forms an essential component while evaluating children with anemia, despite mixed dietary habits and normal MCV.

Keywords: Anemia, B12, children, vitamin

Introduction

Vitamin B12 deficiency in children is a significant preventable public health problem with potential long term neurological consequences, if left undiagnosed.^[1-3] It is often under reported in children from developing countries, with a varying prevalence of 21-45%. Vegetarianism, minimal intake of animal products,

poverty and malnutrition can lead to vitamin B12 deficiency.^[4-6] Paucity of studies reporting vitamin B12 status in sub Himalayan region has lead to the present study of estimating the proportion of vitamin B12 deficient children and evaluating their clinical profile.

Methods

Ethics

The study was done after obtaining ethical clearance from institutional ethics committee [protocol number IEC/18/155/04/01/2018]. The study was designed to confirm

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the Declaration of Helsinki and ICMR guidelines for ethical biomedical research on human subjects. Following Institutional Ethics Committee approval, a patient information document was presented to each patient fulfilling the above mentioned criteria. After explaining pertinent details of the study, a valid informed consent was obtained for assessment according to a pre-designed proforma. Children were managed as per unit protocol.

Study design

This prospective analytical study was conducted in a tertiary care hospital in Northern India, located in the sub-Himalayan region over a period of 18 months [January 2018 to July 2019].

Selection and description of participants

All the consecutive children aged from 1-18 years presenting to outpatient and inpatient clinics of pediatric department with anemia [Hemoglobin <10 g/dl in <6 yrs and <11 g/dl in age ≥6 yrs] were included. Infants were excluded from the study as maternal B12 deficiency can reflect in the offspring when exclusively breastfed. Currently, exclusive breast feeding is recommended up to 6 months of age and a buffer period of 6 more months was given to allow for the accumulation of vitamin B12 from other dietary sources during this period. This institute caters to a mixed population – both from hilly areas and the plains along side, mixed food habits. Regional food products comprised mainly wheat breads, white rice, pulses, salads and vegetables and dairy products. Children who received vitamin B12 prior to enrollment, Children with inborn errors of metabolism, malignancies and those who refused consent were excluded.

Technical details

Study children were evaluated for vitamin B12 deficiency as per the unit protocol. 1.5 ml venous blood was collected in 2 EDTA vials for the complete blood counts [CBC] [by automated analyzer], peripheral smear and serum vitamin B12 levels [by Advia Centaur XP immunoassay systems]. Deficiency of vitamin B12 was defined as serum levels <300 pmol/L.

Statistics

The sample size of 98 was calculated based on the prevalence of 44%, with a power of 80%, a significance level of 0.05 and an allowable error of 10%, [4 pq/L²: 4 × 0.44 × 0.56/0.1 × 0.1] to account for losses a total of 111 children were finally enrolled. Data were expressed as mean and standard deviation [SD] or median and inter quartile range. [IQR] and analyzed in IBM SPSS software version 26. For Qualitative data was analyzed using Pearson Chi square tests and quantitative data was analyzed using two-sided independent samples t tests. On having a significant P value of < 0.05 on these tests, further analysis was done using binomial/multinomial regression analysis to look for odds ratios.

Results

A total of 198 children with pallor were screened for eligibility, of which 111 patients were included [Figure 1] with 64.8% (n = 72)

being vitamin B12 deficient. The median [IQR] age, weight percentile and height percentile of the study population was 9 [1-14] years, 6.7 [2.6-24.1] and 9.7 [1.3-38], respectively [Figure 2]. Median [IQR] serum vitamin B12 levels were: 219.5 pmol/L [130.7-423]. The mean and median values of hematological parameters were given in Table 1.

Most common hematological manifestations in children with vitamin B12 deficiency were leukopenia [38.9%], followed by macrocytosis [37.5%] and thrombocytopenia [34.7%].

Among the 111 children, generalized muscular weakness, [75.7%, n = 84], lethargy in 63.9% [n = 71], weight loss [62.1%, n = 69] and poor appetite [28.8%, n = 32] were the predominant presenting symptoms. Knuckle pigmentation and fragile [brittle] hair were found in one-fourth [25.2%, n = 28] and one-fifth [22.5%, n = 25] of the children, respectively [Table 2].

Neurological manifestations

Neurologic manifestations were found in 22.5% [n = 25] of the study population. Amongst them, majority [60%, n = 15], belonged to 1-2 years age group. Out of 25 children with neurological manifestations, 80% [n = 20] had low serum vitamin B12 levels. The other neurological findings included tremors, movement abnormalities, absent deep tendon reflexes and hypotonia. Seven percent of the study population had behavioral changes [in the form of reduced interaction with the surroundings] which showed statistical significance with vitamin B12 deficiency [p value: 0.02] [Table 2].

Subgroup analysis of infants and children was done with cut off of 6 years. Different parameters were significant in these 2 different age groups.

Subgroup analysis among children aged <6 years

40.5% [N = 45] of the entire study population were younger than <6 years with a mean ± SD age of 1.73 years ± 1.23. The hemogram of these children showed median [IQR]

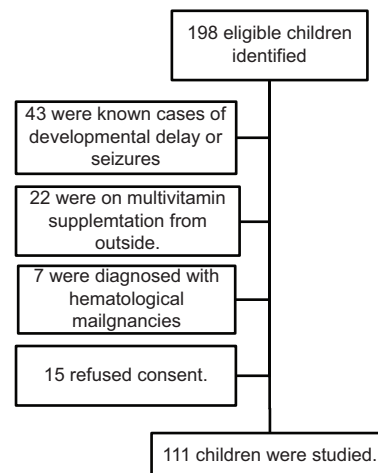


Figure 1: Flow Chart Of Study Participants

Table 1: Clinical And Laboratory Profile Of Study Children

Variable	Age	Height Percentile	Weight Percentile	Hb (g/dL)	TLC (/mm ³)	Platelet (lakhs/mm ³)	MCV (fL)	Vit B12 (pmol/L)
Mean	8.5	22.4	16	6.8	8305.7	2	89.5	380.1
Median	9	9.7	6.7	7	6933	1.5	89	219.5
SD	6.1	27	19.7	3	6155	1.8	22.5	475.3
IQR 25	1	1.3	2.6	4	3935	0.7	74	130.7
IQR 75	14	38	24	10	11230	2.905	107.2	423

haemoglobin levels of 6.5 [4.6-8.57] g/dl, median [IQR] Total leukocyte count 9400 [5985-12870] per cumm, median [IQR] platelets: 2.07, [1.01-3.36] per cumm, median [IQR] MCV levels: 80.8, [57.0-97.7] fL. Median [IQR] serum vitamin B12 levels were 189 [110-374] pmol/L.

The most frequent manifestations were poor appetite [69.7%], muscular weakness [58.1%], fragile hair [40%, n = 18], knuckle pigmentation [35.6%, n = 16] and hypotonia [31.1%, n = 14]. 13.9% [n = 6] were on a vegetarian diet whereas one fourth [26.7%, n = 12] were still being exclusively breastfed. Seven percent had seizures and 9% had tremors. Tremors are a unique manifestation of vitamin B12 deficiency in infants, especially, in the Indian subcontinent, called as infantile tremor syndrome [ITS]. Nine percent of the children came with clinical features simulating ITS. Weight loss, knuckle pigmentation, and hypotonia were significantly more prevalent in vitamin B12 deficiency group [p: 0.001]. Logistic regression showed weight loss to be independently associated with serum vitamin B12 deficiency [p: 0.01]. The odds ratio was highest with weight loss (8.6; 95% CI: 1.564 – 46.88) with vitamin B12 deficient children having 8.6 times higher chance of being underweight when compared to their peers. The odds ratio for the presence of hypotonia was 2.9 (95% CI: 0.233-35.11) and hyper pigmented knuckles was 5.8 (95% CI: 0.506-66.62).

Subgroup analysis of children ≥6 years

59.5% (n = 66) of the entire study population were ≥6 years. Female to male to ratio was 1.5:1 demonstrating a higher incidence of anemia in females as compared to males as children grow older. The median [IQR] age, weight and height percentiles were 14 [11.8 – 15] years, 9.7 [5.5-29], and 12.3 [2.3-38], respectively. Most of the children were either underweight or stunted. Median [IQR] for hemoglobin, 7.05 [4-10] g/dl, TLC: 5383 [2870-9372] per cumm, platelet counts: 1.2 [0.5-2.6] L per cumm and MCV 95 [80 -110] fL. The median [IQR] serum vitamin B12 levels were 224 [133-434] pmol/L.

Amongst the children ≥6 years, generalized muscular weakness [83.3%, n = 55], lethargy [72%, n = 48] and weight loss [66.6%, n = 44] were the most predominant manifestations. Other features included knuckle hyper pigmentation [19.6%], poor appetite [11.7%], abnormal behavior [6%], hypotonia [4.5%], seizures [3%] and impaired sensation of touch [1.5%]. More than one third of the children [36.3%] were on a vegetarian diet. Muscular weakness was significantly associated with vitamin B12 deficiency [p: 0.027], with a trend towards the development of

knuckle pigmentation [odds ratio: 4.34, 95% CI: 0.85 – 22.23]. When means were compared, mean serum B12 levels were significantly associated with age, weight centiles, hemogram, TLC and platelet counts [p: 0.004].

Discussion

The high occurrence of vitamin B12 deficiency in children is of serious concern and a preventable cause of neurological morbidity, similar to congenital hypothyroidism.^{15,6]} Preferential nourishment of the male child over the female child can result in vitamin B12 deficiency in female children and adolescents, who later can transmit this deficiency state to the fetus in the intra uterine period. Maternal vitamin B12 deficiency thus, increases the prevalence of childhood vitamin B12 deficiency.^{17]} Prevalence of vitamin B12 Deficiency was significantly higher in our study when compared to study done by Chhabra *et al.*^{15]} This could be explained by the fact that our institute being a tertiary care referral center in Northern India, children with persistent anemia and not responding to oral iron therapy are referred for further evaluation from nearby health care centers.

Children aged one to eighteen were included and infants were excluded from the study. The median age of the study population was 9 years. Similar mean age [7 years] was reported by Osei *et al.*^{13]} who studied the nutritional status of primary school children in sub-Himalayan region. Infants were excluded from the study, as previous study done in our country by Mittal *et al.*^{17]} showed a remarkable percentage of mothers being deficient in vitamin B12, and consequently leading to deficiency in their breastfed infants. As, standard practice of weaning from breast milk occurs after the age of 6 months, we have included infants of more than one year of age in our study. This allows accumulation of body stores of vitamin B12 from other dietary sources and thus eliminates confounding effect of maternal vitamin B12 deficiency.

There is a bimodal distribution with respect to the prevalence of vitamin B12 deficiency in the study population. The increased incidence in the early age groups suggests that carrying over of in utero deficiency persists longer than 1 year and that 6 months of complimentary food intake is not sufficient to meet the demands of the growing infant. Testing for vitamin B12 deficiency and its supplementation should therefore be done from the beginning of pregnancy in order to prevent long-term effects of its deficiency in the unborn child.^{18-12]} A randomized controlled trial showed

Table 2: Clinical Characteristics And Examination Findings Between Vitamin B12 Deficient And Sufficient Populations n=111

Variables	Vitamin B12 deficient population		Vitamin B12 sufficient population		Chi square p
	Numbers (n)	Percentage (%)	Numbers (n)	Percentage (%)	
Reduced activity	50	45%	21	18.9%	0.292
Weight loss	49	44.1%	20	18%	0.216
Muscular weakness	52	46.8%	32	28.8%	0.048
Seizures	3	2.7%	2	1.8%	0.721
Tremors	4	3.6%	0	0	0.167
Developmental delay	7	6.3%	0	0	0.05
Knuckle pigmentation	25	22.5%	3	2.7%	0.004
Fragile hair	20	18%	5	4.5%	0.281
Hypotonia	14	12.6%	2	1.8%	0.072
Breathlessness	9	8.1%	1	0.9%	0.024
Poor appetite	21	18.9%	11	9.9%	0.088
Behavioural changes	8	7.2%	0	0	0.027
Exaggerated DTR	1	0.9%	0	0	0.3

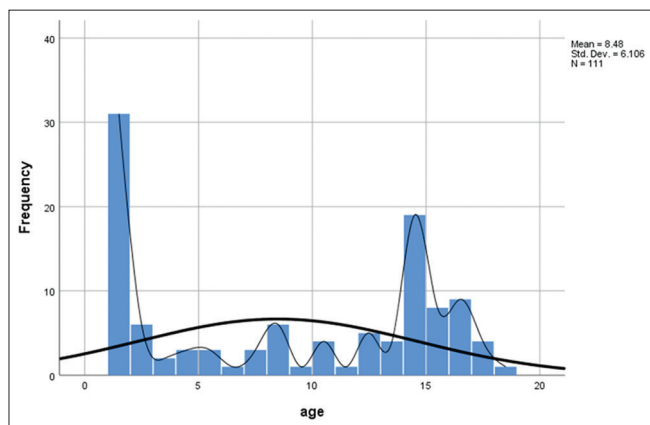


Figure 2: Age Wise Distribution Of Study Participants

that supplementation with oral vitamin B12 during pregnancy and lactation significantly improved the vitamin B12 status of the mothers and their infants.^[13] Since vitamin B12-deficient mothers have vitamin B12-deficient infants, a long period from ‘pregnancy to infancy’ provides numerous windows of opportunity for vitamin B12 supplementation at individual as well as community level to optimize vitamin B12 status and hence the neurodevelopment of infants and children.^[14] Screening and treating of mothers for vitamin B12 deficiency will contribute to the health of both the mother and their feeding infant.^[15] The second peak occurring during mid adolescence can also be explained by the same phenomena of the intake not being able to meet the increased requirements during growth spurt.

Males [51.3%] were marginally more than females [48.6%] in the present study. In a hospital based study similar findings were reported by Goyal *et al.*^[14] Indian families give more attention to males, which may lead to over all higher hospital admission rates in them, leading to male preponderance. 59.4% [n = 66] of the study population was older than 6 years. The female to male ratio in this age group was 1.5:1, demonstrating a higher incidence of anemia in females as compared to males as children grow older.

This corresponds to the demographic data described by Kumari *et al.*^[16] Khanduri *et al.*^[17] and Salma *et al.*^[18]

Among 111 children, lethargy was present as a single major complaint in 63.9% followed by weight loss [62.1%]. This can be explained by the poor appetite that was associated with the presence of anemia, there by setting up a vicious cycle of worsening anemia due to poor nutrient intake and weight loss. Aron *et al.*^[19] reported 27% weight loss in adults with vitamin B12 deficiency, which is much lower than our study. Children seem to encounter weight loss in a greater proportion.

Most of our study population was both stunted and underweight compared to other studies done in this region. Osei *et al.*^[3] found 60.9% prevalence of wasting and 12.2% of stunting among children of age 6-10 years. The mean serum vitamin B12 levels in our study was 380 pmol/L, compared to 463.1 pmol/L reported by Osei *et al.*^[3] for children aged 6-10 years. The serum vitamin B12 levels were comparatively lower in our study population. Kapil *et al.*^[1,2,20] reported median serum vitamin B 12 level as 372 pmol/L in their population, which was comparable with our present study. Our study population of ≥6 years showed a higher level of serum vitamin B12 than the younger [<6 years] counterpart.

Neurological manifestations were present in 22.5% study children. Chhabra *et al.*^[5] reported 11.1% children with neurological manifestations. Aron *et al.*^[19] and Cui *et al.*^[21] found neuropsychiatric and cognitive dysfunction in 3% of their study population. Children who had normal serum B12 levels and neurological manifestations [20%] might be associated with other co morbidities like inborn errors of metabolism which can lead to cellular level deficiency and early neurological involvement.^[22] Vitamin B12 deficiency or insufficiency and elevated homocysteine levels have been associated with the development of depression among children and adolescents in a recent study.^[23]

The prime neurological manifestations comprise of developmental delay, reduced intelligent quotient [IQ], ITS and sub acute combined degeneration of spinal cord. Complaint of developmental delay was found in 6% of our total study population with most of them belonging in the 1-2 year age group. Since most of these children were breastfed and not put on any sort of weaning diet, it can be safely assumed that this is because of maternal deficiency. This association has also been demonstrated by Mittal *et al.*^[7] Therefore, in infants who are exclusively breastfed and present with megaloblastic anaemia or psychomotor retardation, Vitamin B12 levels need to be estimated.^[24] In this study, prevalence of ITS was 10%, which can have profound consequences on the long term cognitive function. Hence, appropriate timely treatment with vitamin B12 in conjunction with nutritional supplementation results in significant improvement in neuro development of the affected children and timely supplementation reduces the socio-economic burden of the society.^[25-30] Likewise, the predominant hematological presentation consists of anemia, leukopenia and pancytopenia. Other clinical features include knuckle hyper pigmentation, weight loss, glossitis and angular cheilitis. Knuckle hyper pigmentation was significantly more prevalent in vitamin B12 deficient group in this study. Thus, it is emphasized to consider vitamin B12 deficiency as a reason of cutaneous hyperpigmentation and also that appropriate treatment leads to its rapid resolution and potential neurological complications can be curtailed.^[31]

A vegetarian diet was present in 27.1% of the children. Majority of the children were on mixed diet. In contrast to the known predisposition of vitamin B12 deficiency in individuals on a vegetarian diet, our study did not find any significant association between vegetarianism and vitamin B12 deficiency. This might be multifactorial. Quantification of animal products intake could not be done in our study. Although the family was accustomed to non-vegetarian food, the child might have been rarely eating non vegetarian diet and could have succumbed to vitamin B12 deficiency. Also, the number of children with gastritis and proton pump inhibitor [PPI] usage and their duration was not evaluated which could have influenced the association of diet and B12 deficiency as prolonged intake of PPIs are a known risk factor for development of vitamin B12 deficiency as demonstrated by Debryune *et al.*^[32]

Vitamin B12 deficiency should be considered in patients with congenital hypotonia, syncope, gait ataxia, convulsions, vision loss or vision blurring, neuropathy, dizziness or tremor, even in the absence of anemia. Children with neurological symptoms should be evaluated for vitamin B12 deficiency with or without associated anemia because nervous system symptoms can precede anemia by months.^[33] Our study is one of the few studies which compared manifestations of vitamin B12 in younger and older children, ascertaining the fact that neurological features occur early when compared to hematological presentation.

A recent study showed that intranasal administration of vitamin B12 in children is safe and effective substitute to intramuscular

injections, leading to higher compliance and less burden to patients.^[34] Further studies are required to evaluate the efficacy of intranasal route of vitamin B12 in children with vitamin B12 deficiency.

Conclusions

Two-thirds of the children are vitamin B12 deficient among the study population with bimodal age distribution. Knuckle pigmentation and fragile hair was seen one-fourth and one-fifth of the children respectively. Nine percent of children with B12 deficiency had NYHA Grade ≥ 3 breathlessness. One-fifth had neurological manifestations. 80% of children with neurological manifestations were found to be severely deficient in vitamin B12 levels. Younger children were underweight while older children were stunted.

Median serum vitamin B12 levels were lower in children aged < 6 years than those ≥ 6 years. Median TLC and platelet counts were lower in children ≥ 6 years than those < 6 years. Contrastingly median MCV was higher in children ≥ 6 years [95 fL] than those < 6 years [80.8 fL]. Most common hematological manifestation in children with vitamin B12 deficiency were leukopenia [38.9%], macrocytosis [37.5%] and thrombocytopenia [34.7%].

Children with vitamin B 12 deficiency are 3.5 times higher risk for behavioral changes. A statistically significant association of knuckle pigmentation and NYHA grade ≥ 3 breathlessness with vitamin B12 deficiency was found (p value: 0.004) with an odds ratio of 7.2.

Children coming to primary care physicians with knuckle pigmentation, fragile hair, weight loss, muscle weakness and anaemia need to be investigated for vitamin B12 deficiency, so that early and appropriate treatment can be initiated which could prevent long term neurological impairment. As the prevalence of vitamin B12 deficiency is as high as 64.8% in this study, we recommend that primary care physicians should have high index of suspicion towards this common, devastating yet preventable condition.

Strengths of our study

Our study included children from a wide age group [ranging from 1-18 years], who were extensively evaluated and severity of vitamin B12 deficiency was correlated with clinical profile. Elaborate statistical analysis was done and children with subclinical vitamin B12 deficiency were identified and timely supplemented.

Limitations of our study

Due to logistic reasons, bone marrow examination, estimation of serum methylmalonic acid and homocysteine levels [Other markers of vitamin B12 deficiency] were not planned in the study.

Future recommendations

Determining the efficacy of intra nasal route of vitamin B12, a newer mode of administration of vitamin B12, in deficient children can be an attractive option for future research.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Key Messages:

- Neurological manifestations are four times more common in children with vitamin B12 deficiency. Prevalence of ITS was remarkably high in this study accounting to 10% and 16.2% of children had global developmental delay.
- More than one-third of the children in the study were on a vegetarian diet (36.3%) and children with delayed weaning were more prone to have vitamin B12 deficiency and neurological features.
- Subtle clinical signs like fragile hair, absent DTR, peripheral hyper pigmentation, and behavioral changes preclude more severe neurological manifestations in children with vitamin B12 deficiency. Hence, these features should prompt the primary care physician to investigate for vitamin B12 deficiency for timely management.
- Neurological manifestations were predominant in younger children [<6 years] and hematological abnormalities were more frequent in older children [≥ 6 years]. Estimation of vitamin B12 levels forms an essential component while evaluating children with anemia, despite mixed dietary habits and normal MCV. Our study concludes that there is a substantial burden of vitamin B12 deficiency in children with anemia in our area which leads to neurological co morbidities.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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