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Original Research Article

Development delay in children with severe acute malnutrition and its association with Vitamin B12 deficiency

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ABSTRACT

Background: About half of the under five children are malnourished in India and so is morbidity associated with it. Malnutrition is also associated with multiple vitamin deficiency one of which is vitamin B12. Vitamin B12 is essential for DNA, RNA and protein synthesis; and for myelination of brain during the early childhood period. Deficiency of vitamin B12 can lead to megaloblastic anemia and neurological problems. So, authors aimed to look prevalence of vitamin B12 deficiency and; its hematological and neurological effects in severe acute malnourished children.
Methods: it was an observational case control study, in which severe acute malnourished (SAM) children aged 0- 59 months who were admitted in Nutritional Rehabilitation Centre (NRC) were enrolled. Vitamin B12 levels were estimated and levels <200 pg/ml, 200-350 pg/ml, and >350 pg/ml were considered deficient, insufficiency and sufficient. Complete blood count was done for hematological effects and; developmental assessment was done to look for neurological effects.
Results: Vitamin B12 was deficient, insufficient, normal in 15(16.3%), 25 (27.5%) and 52 (56.5%) children respectively. Vitamin B12 deficiency was significantly associated with hyperpigmentation and glossitis. Infant and young child feeding practices were not associated vitamin B12 deficiency. Macrocytic anemia was found in 23.4% SAM children and macrocytosis was not significantly associated with vitamin B12 deficiency. Developmental delay was found in 55.3 % children and was not significantly associated with severe acute malnutrition.
Conclusions: There is high prevalence of Vitamin B12 deficiency and insufficiency in children with severe acute malnourished children. Macrocytic anemia and developmental delay are not significantly associated with vitamin B12 deficiency.

Keywords: Child, Nutritional Rehabilitation Center, Severe acute malnutrition, Vitamin B12 deficiency, Macrocytic anemia, Developmental delay

INTRODUCTION

In India, 43.5% children under 5 years of age are underweight. This includes 43% moderate to severe, 16% severe malnutrition, 7.7 % of children are severely wasted children.[1] The of prevalence of vitamin B12 deficiency among children 1-6 years of age is 9.5%, While its prevalence in severe acute malnourished (SAM) children is 37.5%. [2, 3] The common causes of vitamin B12 deficiency are decreased intake like strict vegetarian diet, child born to deficient vegetarian mother, increased metabolism by certain drugs like H2 blockers or proton pump inhibitors, malabsorption like celiac diseases, small intestinal bacterial overgrowth, pernicious anemia and atrophic gastritis. Vitamin B12 deficiency can lead to restlessness, dullness, anorexia, macrocytic anemia (raised mean corpuscle volume), thrombocytopenia, pancytopenia and developmental delay or regression

which may further lead to deterioration of nutritional status of the children because of decreased food intake.[3-5] In first two years of life, brain growth and myelination is very rapid and Vitamin B12 deficiency results in restricted myelination, resulting in various neurological and intellectual problems in children including development delay.

Macrocytic anemia is caused by either vitamin B12 or folate deficiency. Since folate supplementation is given routinely to all SAM children according to World Health Organization (WHO) protocol of management of SAM, it is required to identify prevalence vitamin B12 deficiency and need for its routine supplementation. So, authors aimed to find out the prevalence of vitamin B12 deficiency, its causes and effects in children with severe acute malnutrition.

METHODS

Children with severe acute malnutrition aged 0 to < 59 months admitted Nutritional Rehabilitation Centre (NRC) of a tertiary care centre of eastern Uttar Pradesh state of India, from September 2016 to August 2017 were included in the study. Children with severe acute malnutrition (SAM) 0-59 months of age were defined as 1) Weight for height below -3 standard deviation (SD or Z scores) of the median WHO growth reference and/or 2) Presence of bipedal edema and/or 3) Mid upper arm circumference (MUAC) below 11.5 cm. In a child below 6 months of age all the criteria were same except that MUAC was not included.

The exclusion criteria were 1) Underlying neurological disease like Perinatal asphyxia/ Hypoxic ischemic encephalopathy, cerebral palsy with mental retardation, meningitis or congenital CNS malformations, heart disease, inborn errors of metabolism, children born preterm, and unstable vital parameters (shock, severe respiratory distress, coma).

Complete history and examination were done according to the predefined performa. Developmental assessment was done using Vineland Social Maturity Scale (VSMS). Developmental age (DA) was calculated by VSMS and then Developmental Quotient (DQ) was calculated using the formula: DQ=100 X (Developmental age/Chronological age). DQ less than 70 was considered as developmental delay.

Complete blood count (CBC) was done by the automated cell counter. Serum vitamin B12 level was measured by the standard chemiluminescence assay. (ARCHITECT Plus Analyzer by Abbott Diagnostics). Megaloblastic anemia was defined as MCV (fL) [6]: >108 at birth and >78 for age 0.5-5 years. Depending on the level of vitamin B12, the patients are categorised as under Group I: Vitamin B12 level <200 pg/ml (deficiency), Group II: Vitamin B12 level 200-350 pg/ml (insufficiency) and Group III: Vitamin B12 level >350 pg/ml (adequate).

Statistical analysis

Continuous data were summarized as Mean ± SD (standard deviation) while discrete (categorical) in number and percentage (%). Continuous groups were compared by one factor analysis of variance (ANOVA) and the significance of mean difference between (inter) the groups is done by Newman-Keuls post hoc test after ascertaining normality by Shapiro-Wilk's test and homogeneity of variance between groups by Levene's test. Categorical groups were compared by chisquare ($\chi 2$) test.

RESULTS

One hundred three children were included in our study. The mean age of children was 14.15±10.26 months with a male to female ratio of 1.2:1. Forty one (39.8%) children were in middle lower middle class, 37 (35.9%) to lower upper lower class, 18(17.5%) to upper middle class and 7 (6.8%) to lower class of socioeconomic status according to Kuppuswamy scale.

Sepsis (defined as systemic inflammatory response syndrome{SIRS} and confirmed infection like positive blood, urine or stool culture and chest X ray showing consolidation) (39.8%) was the most common complication and followed by pneumonia in 14 (13.6%), acute diarrhea (10.7%), chronic diarrhea (6.8%), persistent diarrhea (1%), anemia (7.8%) and infantile tremor syndrome (4.9%). Sixty eight (66.0%) children were completely immunized, 34 (32.0%) were incompletely immunized.

Vitamin B12 levels could be done only in 92 children because of some technical error. Vitamin B12 was deficient, insufficient, normal in 15(16.3%), 25 (27.5%) and 52 (56.5%) children respectively.

Early initiation of breast feeding (EIBF), exclusive breast feeding (EBF), timely introduction of complementary feeds (TICF), minimum meal frequency (MMF), and minimum dietary diversity (MDD) was found in 71 (68.9%), 58 (56.3%), 69 (67.0%), 75 (72.8%), 48 (46.6%) children respectively. Sixty six (64.1%) children were vegetarian. Nine (8.7%) children had a history of taking antacids. Other drugs which may cause megaloblastosis were not taken by SAM children and include aspirin, anticonvulsants, colchicine, ethanol and contraceptive hormones. None of the above risk factors were associated with vitamin B12 levels (Table 1). Pallor was found in 74 (71.8%) children, edema was present in 17 (16.5%) children, signs of Vitamin B12 deficiency viz. hyperpigmentation, glossitis or both (hyperpigmentation and glossitis) was present in 20 (19.4%), 31 (30.1%) and 10 (9.7%) children respectively. Hyperpigmentation and glossitis were significantly associated with vitamin B12 levels (Table 2). Edema was present in 18 (19.5%) children. Pallor and edema were not associated with vitamin B12 levels (Table 2).

Table 1: Association of serum Vitamin B12 level with IYCF indicators and drug intake (n=92).

IYCF indicators and drug intake	Group A (n=15) (%)	Group B (n=25) (%)	Group C (n=52) (%)	p value
Vegetarian diet	8 (53.3)	17 (68.0)	35 (67.3)	0.571
Early initiation of breast feedin (68.9%)	11 (73.3)	17 (68.0)	36 (69.2)	0.936
Exclusive breast feeding (56.3%)	9 (60.0)	17 (68.0)	27 (51.9)	0.401
Timely introduction of complementary feeds (67%)	8 (53.3)	17 (68.0)	35 (67.3)	0.571
Minimum dietary diversity (75%)	5 (33.3)	12 (48.0)	25 (48.1)	0.578
Minimum meal frequency (48%)	10 (66.7)	19 (76.0)	40 (76.9)	0.715
Drug intake: Antacids	4 (26.7)	2 (8.0)	3 (5.8)	0.053

Table 2: Association of vitamin B12 levels with clinical signs and symptoms (n=92).

Parameters	Group A (n=15) (%)	Group B(n=25) (%)	Group C(n=52) (%)	p value
Edema	3 (20.0)	3 (12.0)	9 (17.3)	0.768
Pallor	10 (66.7)	18 (72.0)	37 (71.2)	0.931
Signs of vitamin B 12 deficiency				
Hyperpigmentation	4 (26.7)	8 (32.0)	6 (11.5)	<0.001
Glossitis	5 (33.3)	14 (56.0)	9 (17.3)	
Both	6 (40.0)	3 (12.0)	1 (1.9)	
Developmental delay	11 (73.3)	12 (48.0)	29 (55.8)	0.290

Table 3: Association of vitamin B12 levels with hematological parameters.

Hematological profile	Group A (n=15) (%)	Group B (n=25) (%)	Group C (n=52) (%)	p value
Hb (g%)	8.97±1.77	8.86±3.11	8.71±2.33	0.927
MCV (fL)	73.65±12.51	69.92±15.04	72.05±13.73	0.694
TLC (/mm3)	12087±7070	12176±7178	11262±5311	0.793
Platelet count (lac/mm3)	2.03±0.93	2.42±1.45	2.03±1.14	0.396
Pancytopenia	1 (6.7)	2 (8.0)	0 (0.0)	0.130

Sixty seven children (65.0%) were anemic i.e. hemoglobin (Hb) levels <11gm/dL. Among them, 50 (48.5%) children had mild to moderate (7-11 gm/dL) anemia while 17 (16.5%) children were severely anemic (Hb<7 gm/dL). Pancytopenia was found in 3 (2.9%) children.

Macrocytic anemia (mean cell volume {MCV} > 108 fL at birth to 6 months and > 78 fL for age 0.5-5 years) and microcytic anemia (MCV <72 fL) was found in 25 (24.3%) and 52 (50.5%) children respectively. There was no significant correlation between MCV and vitamin B12 levels (Table 3).

Sixty three (61.2%) children had a low RBC count, 5 (4.9%) children had leucopenia and 35 (34.0%) children had thrombocytopenia. The VSMS score, developmental age (DA) (month) and developmental quotient (DQ) (%) of children ranged from 1 to 48, 1 to 44 and 4 to 97 respectively with mean (± SD) 11.70±11.08, 8.48±8.94 and 58.14±25.49 respectively. Fifty five (55.3%) children had developmental delay (DD) with DQ <70. The serum vitamin B12 level was not associated (p>0.05) with developmental delay (Table 4).

Table 4: Developmental assessment of SAM children (n=103).

Developmental profile	No of children (%)
VSMS (score) Mean±SD	11.70±11.08
Developmental age (month) Mean±SD	8.48±8.94,
Developmental quotient (%) Mean±SD	58.14±25.49
Developmental delay (DQ <70)	57 (55.3)
VSMS (score) Mean±SD	11.70±11.08

DISCUSSION

The mean vitamin B12 levels in SAM children were 629.46±551.43 pg/ml. 14.6% children had deficiency (vitamin B12 level <200 pg/ml), 24.3% had insufficiency (between 200-350 pg/ml), and 50.5% had sufficient levels (>350 pg/ml). The dietary risk factors including vegetarianism and IYCF practices were not significantly associated with vitamin B12 deficiency and insufficiency in children with SAM. Macrocytic anemia was not significantly associated with Vitamin B12 deficiency in children with SAM. Hyperpigmentation and glossitis were significantly (p<0.05) associated with low vitamin

B12 levels. Vitamin B12 level does not correlate well with pallor or edema. Developmental delay in children with SAM was found in 55.3%. Vitamin B12 level was not found to be significantly associated with developmental delay in children with SAM.

The strengths of our study were that it was done in an NRC where strict protocols were followed. Limitation of our study was that we could not estimate urinary methylmalonic acid which is a better marker of vitamin B12 levels because of non-availability of this test in our centre.

Sixty eight (66%) children in our study were fully immunized. According to NFHS-4, children with fully immunized status in India were 62% while in Uttar Pradesh its only 51.1%.[7] The most common complication among SAM in our study was sepsis (39.8%) followed by pneumonia (13.6%) and diarrhea (10.7%).The study done by Choudhary M et al found 70.7% children with sepsis followed by diarrhea (60%) and pneumonia (52%) [8]. The study done by Kumar R et al in Rewa found diarrhea (54%) as the most common complication followed by acute respiratory tract infections (27.9%) [9]. Another study done by Meena DK et al (2016) in Kota revealed loss of appetite (57.41%) followed by anemia (50%) as the most common complications.[10] The study done by Dhanlakshmi K and Devi G in Bangalore also showed diarrhea (28.49%) and pneumonia (35.75%) as most common complications.[11]

In our study, vitamin B12 deficiency was present in 16.3% patients while insufficiency was present in 27.2%. Therefore, a total of 43.5 % children had low vitamin B12 levels. The mean vitamin B12 level was 629.46±551.43 pg/ml. The study done by Dubal J (2015) in Gujarat in 1000 children found the prevalence of vitamin B12 deficiency of 9.5 %.[2] Lower prevalence in this study could be because the study group was not SAM. A study done by Goyal S et al (2017) in Udaipur in 80 SAM children showed vitamin B12 deficiency in 37.5 % and insufficiency in 11.25 % children with overall prevalence of low vitamin B12 levels of 48.75% similar to our study.[3] The mean vitamin B12 level in the above study was 353.65 ± 330.76 pg/ml which is much lower than that in our study. This may be because of the small sample size in their study. Another study was done in Delhi by Kapil U and Sareen N (2014) who estimated that the prevalence of cobalamin deficiency was 67.2% for children in the age group 5-11 years and 68.3% for those in the age group 12-18 years.[13]

Macrocytic anemia (high MCV) was not found to be significantly associated with vitamin B12 deficiency. A similar study done by Jain R et al (2012) in Jaipur, Kwok T et al (2002) in Hong Kong and Bhatia P et al (2012) showed no correlation between vitamin B12 levels and MCV in majority of the cases.[13-15] The lower prevalence of macrocytic anemia amongst the cobalamin deficient children in our study could be because of the reason that we did not do serum MMA and homocysteine levels or urinary MMA levels in our study which is a more reliable marker of vitamin B12 deficiency. Furthermore, the higher incidence of macrocytic anemia among children having adequate serum cobalamin levels may be attributed to the presence of folate deficiency. The signs of Vitamin B12 deficiency (hyperpigmentation and glossitis) were significantly associated with decreased cobalamin level. The prevalence of developmental delay in children with SAM was 55.3%. In our study we did not find any association of vitamin B12 deficiency with developmental delay. Studies done by Biancheri et al (2001) in Italy, Graham et al (1992), Jain R et al (2014) and Agarwal N et al (2016) showed association of vitamin B12 levels with developmental delay.[4,5,16,17] This could be because we conducted our study in SAM children in which there is multifactorial cause of developmental delay.

CONCLUSION

About half of the children with SAM have low vitamin B12 levels. Its specific clinical presentation is hyperpigmentation and glossitis. It is not associated with IYCF practices or any drug intake. It's not associated with developmental delay in SAM children.

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