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Original Research Article

Assessing the Relationship between Vitamin B12 Deficiency and Developmental Delays in Children with Severe Acute Malnutrition

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Abstract:

Background and Aim: Given that folate supplementation is routinely administered to all children with severe acute malnutrition (SAM) as per the World Health Organisation (WHO) management protocols, it is essential to assess the prevalence of vitamin B12 deficiency and the necessity for its regular supplementation. The authors sought to investigate the prevalence of vitamin B12 deficiency, along with its causes and effects, in children suffering from severe acute malnutrition.

Material and Methods: 150 the study focused on children aged 0-59 months who are experiencing severe acute malnutrition (SAM). Vitamin B12 levels were assessed, with a threshold of 350 pg/ml identified as deficient, while classifications for insufficiency and sufficiency were also established. A complete blood count was conducted to assess haematological effects, while a developmental assessment was performed to evaluate potential neurological impacts.

Results: Sepsis emerged as the predominant complication, affecting 40% of cases. This was followed by pneumonia in 21 instances, accounting for 14%. Other complications included acute diarrhoea at 11%, chronic diarrhoea at 7%, persistent diarrhoea at 1%, anaemia at 8%, and infantile tremor syndrome at 5%. A total of 99 children, representing 66.0%, received complete immunisation, while 48 children, or 32.0%, were only partially immunised. Pallor was observed in 105 children, accounting for 70% of the sample. Oedema was noted in 25 children, representing 16.6%. Signs of Vitamin B12 deficiency, including hyperpigmentation and glossitis, were found in 26 children (17.3%), 39 children (26%), and 14 children (9.3%) respectively. There is a notable correlation between hyperpigmentation and glossitis with vitamin B12 levels. In the study, oedema was observed in 25 children, accounting for 16.6% of the total population examined. The findings indicate that pallor and oedema do not show a correlation with vitamin B12 levels.

Conclusion: Approximately 50% of children suffering from severe acute malnutrition exhibit low levels of vitamin B12. The clinical features include hyperpigmentation and glossitis. This condition does not correlate with infant and young child feeding practices or the consumption of any medications. There is no correlation between this condition and developmental delay in children with SAM.

Keywords: Children, Macrocytic Anemia, Severe Acute Malnutrition, Vitamin B12 level.

Introduction

Malnutrition represents a physiological state that arises from an imbalance in energy, protein, and other essential nutrients, whether due to deficiencies or excesses. This condition can be characterized as a state where an individual's physiological functions are compromised, rendering them unable to endure the daily stresses of life, alongside hindered growth and development. [1] Severe acute malnutrition (SAM) represents a critical health challenge, impacting nearly 20 million children globally. [2] Severe acute malnutrition (SAM) is characterized by a significantly low weight for height or length, a mid-upper arm circumference of less than 115 mm, or the presence of nutritional oedema. Severe acute malnutrition (SAM) stands as a critical factor influencing both morbidity and mortality rates in low-income nations, particularly contributing to preventable deaths among children under the age of five. [3] Children suffering from severe acute malnutrition face a mortality rate that is nine times greater than that of their well-nourished counterparts. [4] The prevalence of vitamin B12 deficiency in children aged 1-6 years stands at 9.5%, whereas it is significantly higher at 37.5% among those who are severely acutely

malnourished (SAM). [5,6] Vitamin B12 deficiency can arise from several factors, including insufficient dietary intake, particularly in individuals following a strict vegetarian diet. Additionally, children born to mothers who are deficient in this vitamin may also be at risk. Certain medications, such as H2 blockers and proton pump inhibitors, can increase metabolism and contribute to deficiency. Malabsorption issues, which may stem from conditions like coeliac disease, small intestinal bacterial overgrowth, pernicious anaemia, and atrophic gastritis, are also significant contributors to this health concern. A deficiency in vitamin B12 can result in symptoms such as restlessness, dullness, and anorexia, as well as serious conditions like macrocytic anaemia, thrombocytopenia, and pancytopenia. In children, this deficiency may also cause developmental delays or regression, potentially exacerbating their nutritional status due to reduced food intake. [7,8] During the first two years of life, the brain undergoes significant growth and myelination occurs at a rapid pace. A deficiency in Vitamin B12 can hinder this myelination process, leading to a range of neurological and intellectual issues in children, including developmental delays.

The assessment of vitamin B12 status primarily involves the direct measurement of total serum B12 concentration. [9,10] Vitamin B12 serves as a crucial cofactor for methionine synthase and methylmalonyl CoA mutase. Consequently, when individuals experience suboptimal levels of B12 or deficiency, there is a notable accumulation of total homocysteine (tHcy) and methylmalonic acid (MMA). [11] As a result, serum B12, in conjunction with the functional biomarkers serum tHcy and/or MMA, is commonly utilised to assess vitamin B12 status. [12] Macrocytic anaemia arises from deficiencies in either vitamin B12 or folate. Given that folate supplementation is routinely administered to all children with severe acute malnutrition (SAM) in accordance with World Health Organisation (WHO) guidelines, it is essential to assess the prevalence of vitamin B12 deficiency and determine the necessity for its regular supplementation. The authors sought to investigate the prevalence of vitamin B12 deficiency, along with its causes and effects, in children suffering from severe acute malnutrition.

Material and Methods

The study focused on children aged 0 to 59 months who were admitted to the Nutritional Rehabilitation Centre (NRC) of a tertiary care facility in Gujarat, India, due to severe acute malnutrition. Severe acute malnutrition (SAM) in children aged 0-59 months is characterised by specific criteria: 1) a weight-for-height measurement that falls below -3 standard deviations (SD or Z scores) of the median WHO growth reference, and/or 2) the presence of bipedal oedema, and/or 3) a mid-upper arm circumference (MUAC) of less than 11.5 cm. The exclusion criteria included underlying neurological conditions such as perinatal asphyxia or hypoxic ischaemic encephalopathy, cerebral palsy accompanied by intellectual disability, meningitis, congenital central nervous system malformations, heart disease, inborn errors of metabolism, preterm births, and unstable vital signs. A total of 150 children participated in our study.

A thorough history and examination were conducted following the established protocol. The Vineland Social Maturity Scale (VSMS) was utilised for the developmental assessment. The calculation of developmental age (DA) was performed using the VSMS, followed by the determination of the developmental quotient (DQ) through the formula: DQ=100 X (Developmental age/Chronological age). A developmental quotient (DQ) of less than 70 is regarded as indicative of developmental delay. An automated cell counter was utilised to perform the complete blood count (CBC). The measurement of serum vitamin B12 levels was conducted using the standard chemiluminescence assay. Megaloblastic anaemia is characterised by a mean corpuscular volume (MCV) of greater than 108 fL at birth and exceeding 78 fL for children aged 0.5 to 5 years. Patients are classified into Group I based on their vitamin B12 levels. Vitamin B12 levels can be categorised into three distinct groups: Group I indicates a deficiency with levels below 200 pg/ml, Group II signifies insufficiency with levels ranging from 200 to 350 pg/ml, and Group III reflects adequate levels exceeding 350 pg/ml.

Statistical Analysis

The collected data was organised and input into a spreadsheet application (Microsoft Excel 2019) before being exported to the data editor interface of SPSS version 19 (SPSS Inc., Chicago, Illinois, USA). Quantitative variables were characterised using means and standard deviations or medians and interquartile ranges, depending on their distribution patterns. Qualitative variables were reported in terms of counts and percentages. In this study, the confidence level was established at 95%, while the level of significance was determined to be 5% for all tests conducted.

Results

A total of 150 children participated in our study. The average age of the children was 14.24±9.11 months, with a male-to-female ratio of 1.2:1. According to the Kuppuswamy scale, 60 children (40%) belonged to the middle lower class, 54 (36%) to the lower upper lower class, 27 (18%) to the upper middle class, and 9 (6%) to the lower class of socioeconomic status. Sepsis emerged as the most prevalent complication, affecting 40% of

cases, while pneumonia was noted in 21 instances, accounting for 14%. Other complications included acute diarrhoea at 11%, chronic diarrhoea at 7%, persistent diarrhoea at 1%, anaemia at 8%, and infantile tremor syndrome at 5%. A total of 99 children, representing 66.0%, received complete immunisation, while 48 children, or 32.0%, were only partially immunised.

The study revealed that early initiation of breastfeeding occurred in 102 children, representing 68%. Exclusive breastfeeding was observed in 84 children, accounting for 84%. Timely introduction of complementary feeds was noted in 100 children, which is 66.6%. Minimum meal frequency was achieved in 108 children, or 72%, while minimum dietary diversity was found in 69 children, making up 46% of the sample. Children with SAM did not take other drugs that could lead to megaloblastosis, such as aspirin, anticonvulsants, colchicine, ethanol, and contraceptive hormones. The aforementioned risk factors showed no correlation with vitamin B12 levels.

A total of 105 children, accounting for 70%, exhibited pallor. Oedema was observed in 25 children, representing 16.6%. Signs indicative of Vitamin B12 deficiency, such as hyperpigmentation and glossitis, were noted in 26 children (17.3%), 39 children (26%), and 14 children (9.3%) respectively. There is a notable correlation between hyperpigmentation and glossitis with vitamin B12 levels. In a study, oedema was observed in 25 children, accounting for 16.6% of the total population examined. The findings indicate that pallor and oedema did not show a correlation with vitamin B12 levels, as illustrated in Table 1.

A total of ninety-eight individuals, representing 65.33%, were found to be anaemic, with haemoglobin (Hb) levels below 11 gm/dL. In the study, 48 children, representing 48.97%, exhibited mild to moderate anaemia, with haemoglobin levels ranging from 7 to 11 gm/dL. Meanwhile, 47 children, or 47.95%, were classified as severely anaemic, with haemoglobin levels below 7 gm/dL. A total of 5 children, representing 5.10%, were diagnosed with pancytopenia. The analysis revealed no notable relationship between MCV and vitamin B12 levels, as illustrated in Table 2.

A significant proportion of the children studied exhibited haematological abnormalities, with 94 (62.6%) presenting a low red blood cell count. Additionally, 8 (5.3%) were found to have leucopenia, while 48 (32.0%) showed signs of thrombocytopenia. The VSMS score, developmental age (DA) in months, and developmental quotient (DQ) percentages for the children varied widely, with scores ranging from 1 to 48, developmental ages from 1 to 44 months, and DQ percentages from 4 to 97. The mean scores were reported as 11.65 with a standard deviation of 11.10 for VSMS, 8.20 with a standard deviation of 7.25 for DA, and 58.50 with a standard deviation of 26.78 for DQ. A total of 83 children, representing 55.3%, exhibited signs of developmental delay.

Table 1: Association of vitamin B12 levels with clinical signs and symptoms (n=150)

Variables	Group A (n=20) (%)	Group B (n=30) (%)	Group C (n=100) (%)	P value
Edema	4 (20)	4 (13.3)	17 (17)	0.52
Pallor	13 (65)	22 (73.3)	70 (70)	0.10
Signs of vitamin B 12 deficiency				
Hyperpigmentation	5 (25)	10 (33.3)	11 (11)	0.02*
Glossitis	6 (30)	16 (53.3)	17 (17)	
Both	8 (40)	4 (13.3)	2 (2)	
Developmental delay	14 (70)	14 (46.6)	56 (56)	0.36

*** Indicate statistically significance at p≤0.05**

Table 2: Association of vitamin B12 levels with hematological parameters

Hematological profile	Group A (n=20)	Group B (n=30)	Group C (n=100)	P value
Hb (g%)	8.90±1.48	8.78±2.68	8.65±2.67	0.40
MCV (fL)	72.98±11.47	69.48±14.25	72.24±12.14	0.09
TLC (/mm3)	12050±7148	12164±7254	11280±5324	0.14
Platelet count (lac/mm3)	2.03±0.93	2.42±1.45	2.03±1.14	0.22

Statistically significance at p≤0.05

Discussion

SAM leads to a deceleration of organ systems and triggers various physiological and metabolic alterations within the body. Optimal nutrition plays a crucial role in supporting growth and development, and this is particularly true for the brain. [13] The development of the brain initiates during the intrauterine phase and progresses through infancy and childhood.

This process begins with the creation of brain cells, followed by their differentiation and the formation of synapses. [14] In their research, van den Heuvel et al. [15] identified a delay in the development of hospitalised children suffering from severe acute malnutrition (SAM). A wealth of research indicates that deficiencies in B12 and folate are linked to a range of neurological disorders, adverse health outcomes, and potentially premature mortality. [16,17] The interconnected nature of folate and vitamin B12 metabolism indicates that a deficiency in one vitamin could impact the metabolic processes of the other. Vitamin B12 and folic acid play essential roles in the development of the nervous system. Folic acid plays a crucial role in early foetal development, significantly reducing the risk of neural tube defects. Meanwhile, a deficiency in vitamin B12 can hinder early development by disrupting myelination and dendritic formation, potentially leading to inflammation. Neurological symptoms associated with vitamin B12 deficiency can impact the central nervous system, and in severe instances, may have detrimental effects on brain health. [18]

The average vitamin B12 levels observed in children with severe acute malnutrition (SAM) were recorded at 635.32±540.12 pg/ml. Among children, 14% were found to have a deficiency, 24% exhibited insufficiency, while 50% maintained sufficient levels. The analysis revealed that dietary risk factors, such as vegetarianism and infant and young child feeding practices, did not show a significant correlation with vitamin B12 deficiency and insufficiency in children suffering from severe acute malnutrition. In children suffering from severe acute malnutrition (SAM), there was no significant correlation found between macrocytic anaemia and Vitamin B12 deficiency. There was a significant association ($p< 0.05$) between hyperpigmentation and glossitis and low levels of vitamin B12. The relationship between vitamin B12 levels and symptoms such as pallor or oedema is not strongly established. In a recent study, it was reported that 55.3% of children with severe acute malnutrition (SAM) exhibited developmental delays. The study revealed no significant association between vitamin B12 levels and developmental delays in children suffering from severe acute malnutrition (SAM).

The implications of a low vitamin B12 status can be severe, leading to conditions such as pernicious anaemia and cognitive impairment, given the vitamin's crucial role in the myelination of neurones. The delay in cognitive and psychomotor development observed in children experiencing severe acute malnutrition may be attributed to these factors. Research indicates that Vitamin B12 plays a crucial role in child neurodevelopment and is correlated with cognitive performance in school-aged children. [19,20]

In our study, sepsis emerged as the most prevalent complication among individuals with severe acute malnutrition, with pneumonia and diarrhoea following closely behind. A recent study conducted by Choudhary M and colleagues revealed that 70.7% of children diagnosed with sepsis also experienced diarrhoea and pneumonia. [21] A recent study conducted by Kumar R et al in Rewa identified diarrhoea as the most prevalent complication, affecting 54% of participants, while acute respiratory tract infections were noted in 27.9% of cases. [22] A recent study conducted by Dhanlakshmi K and Devi G in Bangalore revealed that diarrhoea occurred in 28.49% of cases, while pneumonia was noted in 35.75%, highlighting these as the most prevalent complications. [23]

Our research revealed that 16.3% of patients exhibited a deficiency in vitamin B12, while 27.2% were found to have insufficient levels of this essential nutrient. Consequently, 43.5% of children exhibited low levels of vitamin B12. The average vitamin B12 level recorded was 629.46±551.43 pg/ml. A study conducted by Dubal J in 2015 in Gujarat, involving 1,000 children, revealed a prevalence rate of vitamin B12 deficiency at 9.5%. [24] A study conducted by Goyal S et al (2017) in Udaipur involving 80 children with severe acute malnutrition (SAM) revealed that 37.5% of the participants had a deficiency in vitamin B12, while 11.25% exhibited insufficiency. The overall prevalence of low vitamin B12 levels was found to be 48.75%, aligning closely with the findings of our study. [25] A recent study conducted in Delhi by Kapil U and Sareen N (2014) revealed alarming statistics regarding cobalamin deficiency. The researchers found that 67.2% of children aged 5-11 years and 68.3% of adolescents aged 12-18 years were affected by this deficiency. [26]

Clinical settings have reported a notable enhancement following the supplementation of vitamin B12. [27,28] In their review, Volkov et al. [29] articulated the concept of the “Master key effect” of vitamin B12 and suggested the need for trials and assessments of vitamin B12 in treating conditions that have not previously been explored. Research indicates that developmental delays persisted for several months following the start of treatment, highlighting the importance of early diagnosis and intervention. [30] There was no significant association found between macrocytic anaemia and vitamin B12 deficiency. Research conducted by Jain R et al (2012) in Jaipur, Kwok T et al (2002) in Hong Kong, and Bhatia P et al (2012) indicated that there was no significant correlation between vitamin B12 levels and MCV in most instances. [26,31,32]

The increased occurrence of macrocytic anaemia in children with sufficient serum cobalamin levels could be linked to underlying folate deficiency. Indicators of Vitamin B12 deficiency showed a notable correlation with lower cobalamin levels. The results of our study can be somewhat applied to children experiencing severe acute malnutrition (SAM) of similar ages in other low-income nations that share comparable socioeconomic conditions and dietary practices.

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.

More research is needed on the potential benefits of higher levels of RUTF fortification or dietary improvement strategies to increase B12 intake during treatment, or of supplementation after treatment of SAM to normalize B12 status.

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