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ORIGINAL ARTICLE

Are We Under-estimating the Frequency of Vitamin B12 Deficiency in Pediatric Population?

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ABSTRACT

Objective: To determine the frequency of vitamin B12 deficiency among admitted pediatric patients having macrocytic anemia and the reasons for their admissions.

Study Design: Descriptive, cross sectional.

Place and Duration of study: Pediatric department of Dr. Ruth K. M. Pfau Civil Hospital Karachi, from April 2017 to March 2019.

Material and Methods: Medical records of patients 1 month to 12 years of age having an MCV higher than 85 fL and hemoglobin below 10.5 g/dl were inducted into the study by non-probability convenient sampling. Cause of macrocytosis was evaluated using history, examination and investigations including levels of serum B12 and Folate. Low serum B12 was defined as a value below 148 pmol/L. Data was analyzed using SPSS version 22.

Results: The total study population consisted of 90 children, out of which majority (95.5%) were found deficient in vitamin B12. 77.7% had concomitant deficiency of folic acid. 52.3% patients with B12 deficiency were male. Mean age was 3.5 years. 54.65% cases had either severe or very severe B12 deficiency. 62.2% of the cases having macrocytosis were related to malnutrition. Most of the remaining 37.7% cases had diseases not associated with macrocytosis as per literature. Most common among them was malaria diagnosed in 11% patients. Concomitant deficiency of vitamin B12 was observed in conditions known as non-megaloblastic causes of macrocytosis like leukemia, Down's syndrome and hemolytic anemia.

Conclusion: Vitamin B12 deficiency was documented in patients irrespective of gender, age or the diagnosis for which the patients were admitted. It was also seen concomitantly in conditions known to have non-megaloblastic macrocytosis.

Key Words: *Anemia, Macrocytic anemia, Megaloblastic anemia, Vitamin B12, Vitamin B12 deficiency*

INTRODUCTION

Macrocytosis is the increase in mean corpuscular volume (MCV) of erythrocytes more than 2 standard deviation of normal. In clinical practice, anemia is classified on the basis of mean corpuscular volume (MCV) into macrocytic, microcytic and normocytic types.[1] Macrocytic anemia, in turn, is categorized as megaloblastic

and non-megaloblastic. Non-megaloblastic macrocytosis may occur secondary to aplastic anemia, red-cell aplasia, myelodysplastic syndromes, myeloid leukemia, liver disease, severe hypothyroidism, reticulocytosis, use of drugs that affect DNA synthesis, such as azathioprine.[2] These non-megaloblastic causes of macrocytic anemia may have a concomitant vitamin B12 deficiency[3] which along with folic acid deficiency, is by far the most common megaloblastic cause of macrocytosis. Megaloblastic anemia, the more common of the two classes of macrocytosis, therefore should not be taken as a final diagnosis and a cause for the condition must be sought in order to avoid the undue delay in treatment with its consequences.[2]

Being vital to normal neurologic function, red blood cell production, and DNA synthesis, vitamin B_{12} deficiency usually presents with various hematological, gastrointestinal and neuropsychiatric manifestations.[4] Heterogeneity in clinical presentation may lead to difficulty in diagnosis and delay in treatment. Clinical presentation of deficiency may not be obvious thus leading to complex issues around diagnosis and treatment.[5] Though the manifestations usually resolve completely following vitamin B12 supplementation at an early stage, prolonged deficiency may lead to permanent neurologic damage which signifies the need for early diagnosis and treatment.[6]

Vitamin B12 deficiency has increased over the last few decades**,** affecting people of all ages, gender, ethnic, economic and geographical backgrounds. There has been increase in reports of pancytopenia associated with Vitamin B12 deficiency and among cases of pancytopenia, macrocytic anemia stands as important cause, commonest in some series.[7] According to a study done in Pakistan in 2017, the prevalence of vitamin B12 and folate deficiency was 52.4% and 50.8%, respectively, in women of child bearing age.[8] Study done in Lahore, Pakistan showed that among children with anemia, B12 deficiency was found in 64% of patients.[9] Studies on bone marrow histopathologies show that 15-25% of children presenting with pancytopenia are diagnosed as megaloblastic anemia secondary to B12 and folate deficiency.[10] This reflects the delay in diagnosis of this treatable and preventable entity.

There is very limited recent literature available on the frequency of vitamin B12 deficiency in pediatric age group in Pakistan. Knowing the frequency we can recommend strategies including screening of pediatric population for its deficiency and initiating measures to control and prevent its consequences. Along with identification of the causes, it will go a long way in decreasing the morbidities related to its delayed or misdiagnosis and treatment. We, therefore, designed this study to determine the frequency of its deficiency among pediatric patients admitted with macrocytic anemia and to identify the reasons for their admission in pediatric ward in a tertiary care hospital.

MATERIAL AND METHODS

This descriptive study was carried out in the Department of Pediatrics, Dr. Ruth K.M Pfau Civil Hospital Karachi. Exemption from Institutional Review Board (IRB) was taken prior to the study. We reviewed the medical records of patients who were 1 month to 12 years of age, of both genders, who were admitted in pediatric ward with macrocytosis and anemia from April 2017 to March 2019. Anemia was defined as hemoglobin level below 10.5 g/dL as per WHO criteria and macrocytosis was defined as mean corpuscular volume (MCV) more than 85 fL. The data was recorded on a predesigned proforma which included age, gender, hemoglobin, MCV, provisional diagnoses made at the time of admission, and final diagnoses. Investigations, which were done to determine the cause of macrocytosis including peripheral blood smear, serum B12 level and serum Folate level were noted as well as bone marrow histopathology findings, where available. Other investigations relevant to the diagnosis were also recorded.

We defined low serum B12 as a value below 148 pmol/L and low serum Folate as below 5 ng/ml. Patients found deficient in vitamin B12 were further classified into very severe, severe, moderate and mild based on their blood levels 31-60 pmol/L, 61-90 pmol/L, 91-120 pmol/L, 121-148 pmol/L respectively. Cases where the information leading to the diagnosis was not complete in any way were excluded from the study. All the data

was recorded in anonymous format. The data was analyzed using SPSS version 22.0. Descriptive statistics were used for computing frequency and percentage.

RESULTS

The total study population consisted of 90 children, out of which an overwhelming majority 86/90 (95.5%) were found deficient in vitamin B12. 70 out of these 86 (77.7%) had concomitant deficiency of folic acid while remaining 16 (17.8%) had isolated B12 deficiency (fig 1).

52.3% (n=45) patients with B12 deficiency were male, while remaining 47.6% (n=43) were female (p value = 0.33). 80.2% of them were among 1 to 5 years of age, 17.4% were more than 5years of age and 2% were less than 1 year of age. Mean age was 3.5 years with a range of 5 months to 11.5 years (p value = 0.27) (table 1). P values for both age and gender were not significant.

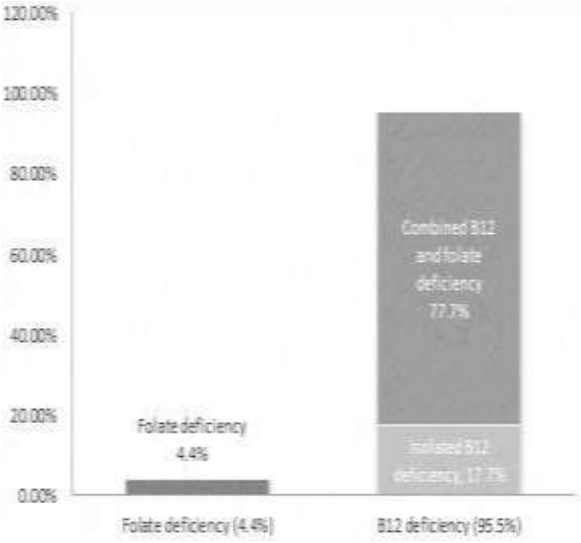

Fig 1: Vitamin B12, Folic acid and Combined (B12 and Folic Acid) Deficiency (n=90)

TABLE 1: Demographic features of patients with Vitamin B12 deficiency

Age Groups	Gender		Total (%)
	Male (%)	Female (%)	
Age less than 1 year	2 (2.3)	0 (0.)	2 (2.3)
Age 1 to 5 years	35 (40.6)	34 (39.5)	69 (80.2)
Age more than 5 years	8 (9.3)	7 (8.1)	15 (17.4)
Total	**45 (52.3)**	**41 (47.6)**	**86 (100.0)**

Assessment of vitamin B 12 levels for severity of deficiency revealed that 47 (54.65%) out of these 86 deficient patients had either severe or very severe deficiency. The remaining 4/90 (4.4%) patients had isolated folic acid deficiency (fig 2).

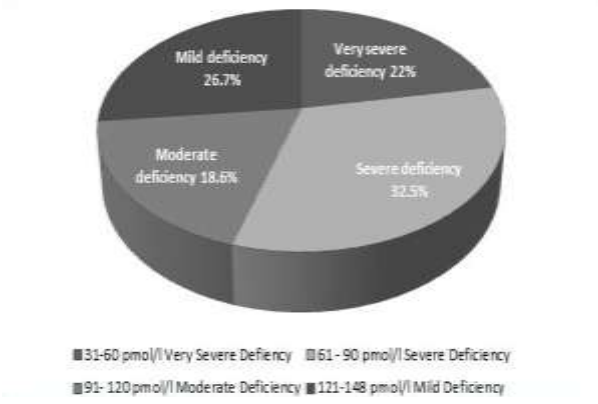

Fig 2: Categorization of severity of Vitamin B12 deficiency

Detailed analysis of diagnoses of the 90 patients who had high MCV revealed that 56 (62.2%) were diagnosed with malnutrition. 36 out of these 56 (64.28%) had primary malnutrition while 20/56 (35.71%) had secondary malnutrition consequent to chronic diarrheas including celiac disease. Most of the remaining 34 cases out of the 90 (37.7%) were diagnosed with diseases not primarily associated with macrocytic anemia as per literature. Most common among them was malaria diagnosed in 10 (11%) patients. Interestingly, all these 34 cases had incidental and coexistent deficiency of either B12, folic acid or both of them, as detailed in table 2.

Another interesting observation that emerged during the analysis was the concomitant deficiency of vitamin B12 in conditions which are actually included in the non-megaloblastic causes of macrocytic anemia. That included three patients of leukemia, two patients of Down syndrome and one patient of hemolytic anemia.

TABLE 2: Coexistence of vitamin B12 and folic acid deficiency with admitting diagnosis

Primary diagnosis	n = 90 (%)	Combined	B12 deficiency	Folic acid deficiency
Nutritional Anemia:				
Primary malnutrition	36 (40.0)	23	10	3
Secondary malnutrition (Celiac disease/Chronic diarrhea)	20 (22.2)	18	1	1
Malaria	10 (11.1)	9	1	-
Other Infections (Dengue 1, TORCH infection 1, Sepsis 3)	5 (5.55)	5		
Lower Respiratory Infections	5 (5.55)	4	1	-
CNS conditions (Cerebral abscess, neurodegenerative disorder, status epilepticus, meningitis, febrile fit)	5 (5.55)	4	1	-
Leukemia	3 (3.33)	2	1	
Down syndrome	2 (2.22)	1	1	-
Miscellaneous (nephrotic syndrome, rat bite, hemolytic anemia, jaundice)	4 (4.44)	4	-	-
Total	**90**	**70**	**16**	**4**

DISCUSSION

In our study sample of 90 patients, an overwhelming majority of 86/90 (95.5%) were found deficient in vitamin B12. Although this finding is compatible with most reports from other researchers, the frequency of 95.5% is way too high in comparison to their results. The reported frequencies vary from 19.4% in Turkish children[1] to 46.6% in Indian adolescents[10] and 45% in children of another city in Pakistan.[9] High frequency is not limited to pediatric population only but is found in adults too. Deficiency in mothers can have a direct impact on the vitamin B12 status of infants. Taşkesen et al reported vitamin B12 deficiency in 72% of the mothers in their region.[11] Similarly in Pakistan, 52.4% of women of reproductive age are deficient in vitamin B12.[8] Thus the deficiency in children is expected.

Among the patients with B12 deficiency, 52.3% were male and remaining was female. Most of the studies in literature reported significant male predominance among pediatric patients with vitamin B12 deficiency[11,12] though female predominance has also been reported by one researcher.[13]

Majority of the patients with B12 deficiency n=69 (80.2%) were between the ages of 1 to 5 years with a mean age of 3.5 years. While the mean age of patients with B12 deficiency found in Lahore, Pakistan was 7.3 months.[9] Similar findings were observed in Turkey where mean age was 13.04 months.[11] This difference is explainable by the fact that they included children up to 2 years of age while we included all pediatric patients 1 month to 12 years of age. On the other hand, another study reported mean age of B12 deficient children as 5.6 ± 5.9 years, again due to including a comparatively wider age range of 1.4 to 17 years.[13] Lack of significant association between vitamin B12 levels and age of children is corroborated by literature review which revealed that the deficiency is affecting population of all ages including infants, toddlers,[11] school age children,[13] adolescents[12] and adults.[4,14,15]

Analysis of our data for severity of deficiency revealed that almost 50% (47/86) of the deficient patients had either severe or very severe deficiency. This severity is higher than that reported in a study done on adult Pakistani population in 2014, where severe vitamin B12 deficiency was found in 24.7% of the subjects.[14] This shows that along with frequency, severity is also increasing with time in the population.

Majority of the subjects with macrocytosis {56/90 (62.2%)} were admitted with the diagnosis of nutritional anemia with primary or secondary malnutrition. Similar observation was voiced by other authors regarding malnutrition being the most common cause of vitamin B12 deficiency in children and mothers especially in developing countries.[16] Molloy et al has also documented dietary deficiency in mothers as the most common cause of vitamin B12 deficiency in infants.[17]

Parasitic infection of intestine, congenital heart

diseases, myelodysplasia and use of medications like anticonvulsant and immunosuppressive agents have been reported in literature as causes of macrocytosis,[3,17,18] but no such patients were found in our study.

In our study, 77.7% of patients had combined deficiency of both vitamin B12 and folic acid which is similar to the findings reported in an infant population of Lahore, Pakistan with 75% of them having low folic acid levels and 64% having decreased Vitamin B12 levels.[9] This phenomenon of coexistent deficiencies is well known and according to published literature, the shared metabolism of folic acid and vitamin B12 suggests that deficiencies in one vitamin may alter the metabolism of the other.[19] We did not look for concomitant iron deficiency in our sample population but this is also well known in literature.[20]

Interestingly the concomitant deficiency of vitamin B12 was observed not only with other nutrient deficiencies but also with non-megaloblastic conditions which are otherwise known to be associated with macrocytosis. In our sample this included three patients with leukemia, two patients of Down syndrome and one of hemolytic anemia, all of whom were deficient in vitamin B12, thus emphasizing the importance of screening all patients of macrocytosis for B12 deficiency.

Limitations of study: This was a single center, retrospective study in a public sector hospital. Prospective, multi-center studies are needed to determine the prevalence of vitamin B12 and folic acid deficiency as well as their long term outcome.

CONCLUSION

Vitamin B12 deficiency is the most common cause of macrocytosis in pediatric population, irrespective of gender, age or associated diagnosis for which the patients were admitted. Conditions known to have non-megaloblastic macrocytosis also had concomitant vitamin B12 deficiency. Folic acid deficiency was also seen frequently with most patients having coexistent B12 deficiency.

Recommendations: Medical professionals and health ministry should seriously consider the merit of early screening of vitamin B12 deficiency and develop and implement strategies to improve vitamin B12 and folic acid intake among children.

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