SHORT COMMUNICATION

Gastrointestinal Abnormalities in Vitamin B_{12} Deficient Patients with Megaloblastic Anemia

Saira Perwaiz Iqbal[1], Ghulam Nabi Kakepoto[2] and Saleem Perwaiz Iqbal[3]

ABSTRACT

In a retrospective cohort study, hospital records of 220 patients (119 males and 101 females, age 1 year-80 years) with megaloblastic anemia were examined to find out any relationship of gastrointestinal abnormalities with vitamin B_{12} and folate deficiencies in these patients. Forty three percent of the patients were folate-deficient (serum folate levels $\leq$ 3.5 ng/ml), while 79% were vitamin B_{12}-deficient (serum B_{12} levels $\leq$ 200 pg/ml). Gastrointestinal abnormalities (gastritis, malabsorption and infection) in B_{12}-deficient patients were marginally significant (p=0.05) compared to the abnormalities in B_{12}-normal patients. Severe dyserythropoiesis was more common in vitamin B_{12}-deficient and folate-deficient patients compared to B_{12}-normal and folate-normal patients. However, the proportions were not statistically significant. Marginally significant occurrence of gastrointestinal abnormalities in vitamin B_{12}-deficient subjects points towards the notion that poor dietary intake along with poor gut absorption could be contributing to the high prevalence of vitamin B_{12} deficiency in this population.

Key words: *Cobalamin deficiency. Folate deficiency. Gastrointestinal abnormalities. Megaloblastic anemia. Vitamin B12 deficiency.*

Vitamin B_{12} deficiency has been found to be a major cause of megaloblastic anemia.[1] Only 1% of the total B_{12} deficient patients studied at the Aga Khan University Hospital (AKUH) were purely vegetarians.[1] Since the amount of vitamin B_{12} in the omnivorous diet is usually in excess of the daily requirements, other factors such as inadequate binding, impaired transport or defective absorption could result in megaloblastic anemia.[2] Considering that various gastrointestinal (GI) abnormalities, in addition to nutritional deficit, could be contributing to B_{12} deficiency in this patient population, investigating the relationship (if any) of these abnormalities with folate and B_{12} deficiencies was embarked upon. Moreover, it was also intended to study any relationship of bone marrow changes with deficiencies of these two vitamins.

For this retrospective cohort study, records of 220 patients (age 1 year-80 years) with macrocytic anemia, who were treated for B-vitamin deficiency at the Hematology Clinic of the AKUH from January 1989 to June 2004, were collected. Exclusion criteria have been described previously.[1] The diagnosis of macrocytic anemia was based on a complete blood count (mean corpuscular volume > 96 fl), history and physical examination. Serum levels of folic acid and vitamin B_{12} had been carried out by the Dual Count Kit (Diagnostic Products Corporation, Los Angeles, CA, USA). Vitamin B_{12} deficiency was defined as serum levels of $B_{12} \leq 200$ pg/ml. Folate deficiency was defined as serum levels of folic acid $\leq$ 3.5 ng/ml. Bone marrow examinations of 123 patients were available and revealed varying degrees of megalobastosis. GI problems associated with megaloblastic anemia were taken into account for any relationship with folate and/or vitamin B_{12} deficiency. The study had been approved by the Ethics Review Committee of the Institution. All analyses were performed on SPSS (Statistical Package for Social Sciences), Software Version 16 for Windows. Test of proportions using chi-square was employed to compare the degree of megaloblastosis and GI abnormality with vitamin status of the patients. P-value < 0.05 was considered significant.

Bone marrow examination revealed that most of the patients (63.4%) had marked dyserythropoietic changes. Nearly one-third of the patients had accompanying GI abnormalities, such as gastritis, malabsorption and infectious gastritis. Percent folate and vitamin B_{12} deficiencies were 43% and 79%, respectively. As shown in Table I, total GI abnormalities in vitamin B_{12}-deficient patients were marginally significant compared to abnormalities in vitamin B-normal patients (p=0.05). Total GI abnormalities in folate-deficient subjects are higher compared to abnormalities in folate-normal patients. However, the proportions were not significantly different. Severe dyserythropoiesis was more common in folate-deficient

[1] *Department of Internal Medicine, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore.*

[2] *Department of Pathology and Microbiology/Paediatrics and Child Health[3], The Aga Khan University, Karachi.*

***Correspondence:** Dr. Saira Perwaiz Iqbal, Department of Internal Medicine, Shaukat Khanum Memorial Cancer Hospital, 7-A, Block R-3, Johar Town, Lahore.*
E-mail: cyra_iq@yahoo.com

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Table I: Frequency distribution of bone marrow and gastrointestinal (GI) changes in anemic patients with respect to their folate and vitamin B_{12} status.

	No.	Number of patients with bone marrow changes n (%)			No.	Number of paitents wtih GI chnages n (%)				
Vitamin status	(n)	Normoblastic erythropoiesis	Mild dyserythropoiesis	Severe dyserythropoiesis	(n)	No. abnormality	GI abnormality Gastritis	Malabsorption	Infection	Total of GI abnormalities
Folate										
Normal	45	3 (6.7)	15 (33.3)	27 (60)	73	52 (71.2)	5 (6.8)	2 (2.7)	14 (19.2)	21 (28.8)
Deficient	34	0	10 (29.4)	24 (70.5)	56	34 (60.7)	7 (12.5)	4 (7.1)	11 (19.6)	22 (39.3)
Vitamin B_{12}										
Normal	22	3 (13.6)	7 (31.8)	12 (54.5)	42	32 (76.2)	3 (7.1)	1 (2.4)	6 (14.3)	10 (23.8)
Deficient	86	5 (5.8)	21 (24.4)	60 (69.8)	153	92 (60.1)	14 (9.1)	13 (8.5)	34 (22.2)	61 (39.9)*

**Marginally significant (p=0.05) when the percent total GI abnormalities in vitamin B_{12}-deficient subjects were compared with abnormalities in vitamin B_{12}-normal subjects.*

and vitamin B_{12}-deficient patients compared to vitamin B-normal patients. However, the proportions were not statistically significant (Table I).

Since a good number of the patients in the population under study belonged to a relatively affluent socio-economic class, nutritional inadequacy may not be the only cause of B_{12} deficiency. Normally, humans maintain a large vitamin B_{12} reserve, which can last upto 5 years. Various GI abnormalities such as, malabsorption, infection and gastritis could be factors interfering with the absorption of vitamin B_{12}.[3] Giardiasis is one of the common causes of water-borne intestinal parasitic infection in Pakistan and is known to cause malabsorption and even significant weight loss in children.[4] It is likely that patients with clinically overt or subclinical infection with *Giardia lamblia* also develop vitamin B_{12} deficiency along with malabsorption of other nutrients. About 9.1% patients had malabsorption and vitamin B_{12} deficiency. They were diagnosed with vitamin B_{12} deficiency only when they were seen in the clinic at the AKUH. Many patients with subtle symptoms or no symptoms due to giardiasis are seen in the community by general practitioners and most probably not checked specifically for vitamin B_{12} or folate levels. Thus, the frequency of vitamin B_{12} or folate deficiency associated with malabsorption is likely to be quite high in the Pakistani population, especially in areas where clean water supply is scarce.

The data showed that GI abnormalities were more commonly observed in patients with vitamin B_{12} deficiency compared to patients with normal levels of vitamin. The classic disorder is pernicious anemia; an autoimmune disease that affects the gastric parietal cells. Destruction of these cells can lower the production of intrinsic factor and subsequently limit vitamin B_{12} absorption. Intrinsic factor antibody is only 50% sensitive but it is more specific for diagnosis. Four patients with gastritis and other neurological symptoms were screened for intrinsic factor antibodies. However, none turned out to be positive. This again indicates that pernicious anemia is not likely to be very common among the studied patient population. Protein-bound vitamin B_{12} in food is cleaved and released in an acidic medium. Any process that interferes with gastric acid production can lead to impaired breakdown; e.g. atrophic gastritis, with resulting hypochlorhydria, subtotal gastrectomy and prolonged use of H2 receptor blocker or proton pump inhibitors. Routine and prolonged use of proton pump inhibitors by the general practitioners in patients with symptoms of gastritis is common in Pakistan. Furthermore, availability of such medicines over the counter and self-medication by the patients for these symptoms is also observed. Vitamin B_{12} deficiency is likely to be quite frequent in such patients. Further studies need to be conducted for screening subclinical B_{12} deficiency in patients receiving long-term acid-suppression therapy. Present results conform well to those reported by Khunduri and Sharma who have reported vitamin B_{12} deficiency to be 65% in a hospital-based population in Delhi and anorexia and gastritis to be among the predominant symptoms.[5] Other less common etiologies include peptic ulcer disease, Whipple's disease, Zollinger-Ellison syndrome, Crohn's disease, intestinal surgery and bacterial overgrowth.

We recommend that screening of vitamin B_{12} and folate should be carried out in patients presenting with gastritis, GI infections or malabsorption.

REFERENCES

1. Kakepoto GN, Iqbal MP, Iqbal SP. Megaloblastic anemia is a hospital-based population. *Med Sci Res* 2000; **28**:45-7.
2. Gibson RS. Principles of nutritional assessment. Oxford, *Oxford University Press*; 990; 461-86.
3. Carmel R. Nutritional vitamin B_{12} deficiency: Possible contributory role of subtle vitamin B_{12} malabsorption. *Ann Int Med* 1978; **88**:647-9.
4. Younas M, Shah S, Talaat A. Frequency of *Giardia lamblia* infection in children with recurrent abdominal pain. *J Pak Med Assoc* 2008; **58**:171-4.
5. Khanduri U, Sharma A. Megaloblastic anaemia: prevalence and causative factors. *Natl Med J India* 2007; **20**:172-5.