Original Research Paper

Volume - 11 | Issue - 10 | October - 2021 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Pediatrics

CASE SERIES OF MEGALOBLASTIC ANEMIA DUE TO VITAMIN 12 DEFICIENCY IN A TERTIARY CARE TEACHING HOSPITAL

Dr. Seema Soni* Associate Professor, PCMC'S PGI,YCMH, Pimpri, Pune-18. *Corresponding Author

Dr. Sandhya Haribhakta Associate Professor, PCMC'S PGI, YCMH, Pimpri, Pune- 18.

Dr Deepali Ambike Professor, PCMC'S PGI,YCMH, Pimpri, Pune-18.

Dr Vineet Rathod Resident ,Pediatrics PCMC'S PGI,YCMH, Pimpri, Pune-18.

ABSTRACT We report herein an interesting case series of pediatric patients presenting with vitamin B12 deficiency. It includes eight patients admitted with us from 15th November 2020 to 15th January 2021.Our patients can be classified into less than or equal to 2 years age group and those more than or equal to 10 years age group, for having different clinical presentation. Out of the 8 patients,5 were females and 3 were males. In a span of less than 2months (post covid situation with economic crisis), these patients from low socioeconomic strata presented in emergency department with severe anaemia with or without neurological involvement. All patients were either exclusively breast fed or vegetarians. Vitamin B12 deficiency may lead to serious neurological deficits in addition to megaloblastic anaemia. Persistent neurological damage can be prevented with early diagnosis and treatment. We believe that a thorough clinical and neurological assessment might prevent failure to notice rare but possible vitamin B12 deficiency in infants with neurological deficits and neurodevelopmental retardation.

KEYWORDS : Megaloblastic anemia, Vitamin B12 deficiency

INTRODUCTION

Megaloblastic anaemia causes macrocytic anaemia from ineffective red blood cell production and intramedullary haemolysis. These are a group of disorder that are caused by impaired DNA synthesis. RBCs are larger than normal at every developmental stage. There is maturational asynchrony between nucleus and cytoplasm of erythrocytes. Myeloid and platelet precursors are also affected. The peripheral blood smear is notable for large oval RBC's with increased mean corpuscular volume. The most common causes are folate (vitamin B9) and cobalamin (vitamin B12) deficiency. Less frequent causes include congenital disorders (inborn errors of metabolism), drugs (particularly chemotherapeutics, folate antagonists, etc.), micronutrient deficiencies and nitrous oxide exposure [1].

Vitamin B_{12} is produced by microorganisms and is found almost exclusively in foods of animal origin. The recommended daily intake is 0.4 µg/day at age 0-6months,0.5 µg/day at age 6- 12months,0.9 µg/day at age1-3 years,1.2 µg/day at 4-8 years,1.8 µg/day at age 9-13years and 2.4 µg/day at age 14-18 years [2,7]. Dietary deficiency of vitamin B_{12} occurs less frequently than folate deficiency because body stores can last for years owing to efficient enterohepatic recycling mechanisms.

Although uncommon, dietary B_{12} deficiency can occur even in industrialized countries in strict vegans and vegetarians, or in breastfed infants of mothers with vitamin B12 deficiency[7].

Criteria for inclusion of patients for the study

1. Patients were assigned socioeconomic status according to modified Kuppuswamy scale. 2.serum B12 level less than normal value 2oo-800pg/ml
3. complete blood count with MCV >97femtolitre
4. clinical features of megaloblastic anaemia like knuckle pigmentation, glossitis, bald tongue 5.no history of any medications

Case presentation

Case 1- 12 years old female, came with vomiting and pain in abdomen for 1 week. Patient had history of weight loss and acute gastroenteritis. There was a past history of decreased appetite since last 6 months. There is no significant birth history or developmental history. On examination, she had severe pallor, icterus, but no lymphadenopathy or organomegaly. On investigation patient had pancytopenia and elevated SGOT. Serum LDH was increased. There were no neurological signs.

Case2 - 1 year old female child, exclusively breast fed, came in emergency dept with history of loose motions, vomiting and fever. She had severe dehydration, convulsion, respiratory distress and pallor. Child had bleeding from injection site, bilious vomiting. Child was given slow infusion of bolus over one hour, injection phenobarbitone. She received packed red blood cell transfusion as well as platelet concentrate. Bone marrow aspiration done showed megaloblastic changes. This child had left side hemiparesis, hypertension. MRI showed ill-defined enhancement in the left temporal cortex, right frontal and parietal cortex, right caudate nucleus, right lentiform nucleus, right corona radiata and the left frontal cortex.

Case3- 12 years old female, vegetarian presented with bilious vomiting and facial edema since 8days.There was a history of loss of weight and appetite since 1month.On examination, patient had pallor and facial edema. There was no hepatosplenomegaly or lymphadenopathy. There were no neurological signs. On investigation patient had pancytopenia. Bone marrow was done, suggestive of megaloblastic anemia.

Case 4- 10 years old female child came with complaints of generalized weakness, vomiting and history of weight loss over 2months.On examination had severe pallor, icterus and knuckle pigmentation. On investigation patient had bicytopenia. Her symptoms resolved with Vitamin B12 therapy.

Case 5- 6months old male patient born of 3degree consanguineous marriage, a full term home delivery, exclusively breast fed presented with fever and cough since 6days.Developmentally patient had regression of milestones. His anthropometric measurements were below thirdpercentile. On admission patient had tachycardia, pallor and hepatomegaly of 2cms.There was no lymphadenopathy or splenomegaly. Patient had pancytopenia.

Case 6- 12 years old male child, 2degree consanguineous marriage, presented with vomiting, decreased appetite, yellowish discoloration of eyes and passing high colored urine. On admission patient had pallor, icterus and clubbing. There was no lymphadenopathy or organomegaly. Knuckle pigmentation was present. Bone marrow aspiration was done. Vomiting subsided after injection Vitamin B12.

Case 7- 2 years old male child, born of non- consanguineous marriage, full term normal delivery with NICU stay of 4days, exclusively breast fed not tolerating the complementary feeding and vomiting thereafter presented with loose motions and vomiting, severe dehydration and metabolic acidosis. He had pallor, no icterus, no hepatosplenomegaly.

Case 8- 1year old female child, full term normal delivery, born of non-consanguineous marriage, exclusively breast fed, not tolerating the complementary feeding and vomiting thereafter presented with history of excessive sleepiness and up rolling of eyeballs with one episode of vomiting. There is history of regression of the milestones. She had failure to thrive, pallor and hepatomegaly. There was no splenomegaly or lymphadenopathy.

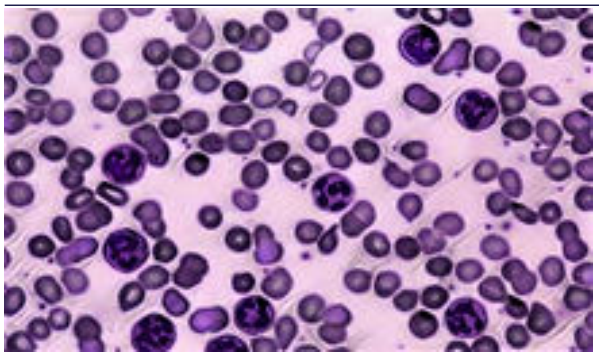

Fig1-peripheral smear of megaloblastic anemia

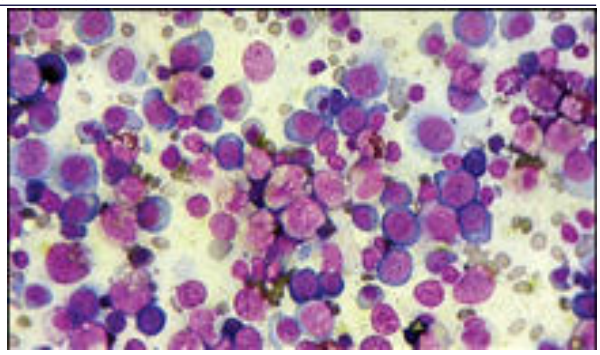

Fig2-Bone marrow in megaloblastic anemia

Table 1: Case-wise lab Investigations

Table 1: Case-wise lab Investigations										
CASES	**CASE 1**	**CASE 2**	**CASE 3**	**CASE 4**	**CASE 5**	**CASE 6**	**CASE 7**	**CASE 8**	**Average**	**SD**
HB GM%	5.5	2.37	3.61	5.9	7.6	4.75	7.6	3.57	5.11	1.91
TLC per cumm	2590	3060	3310	4540	16000	2760	4460	14300	6377.50	5480.60
PLATELET COUNT per cumm	102000	47000	18000	63900	36500	24000	155000	75800	65275.00	45689.16
MCV fL	98	101	97	102	95	114	96	103	100.75	6.09
RETICOUNT %	1.20%	1.00%	0.50%	2%	1%	1%	0.10%	6%	0.02	0.02
HCT %	18.1	9.18	11	16.3	31	15.3	34.3	14.5	18.71	9.10
VIT B12pg perml	83	84	211	83	83	83	83	83	99.13	45.21
IRON	67	131	40	117	24	223	210	200	126.50	78.67
SR FERRITIN	17	38	120	116	233	106	62	98	98.75	66.06
BLOOD GR	B+	A+	A+	A+	AB+	O+	O+	B+	--	--
LDH	3423	3468	3207	2704	2347	2342	2100	936	2565.88	840.93
PBS	Dimorphic Anemia	Macrocytic Normochromic Anemia	Dimorphic Anemia	Macrocytic Anemia With Pancytopenia	Dimorphic Anemia	Macrocytic Normochromic Anemia	Normocytic Normochromic Anaemia	Macrocytic Normochromic Anemia	--	--

RESULTS

Our case series includes 8 patients out of which 5(62.5%) were girls and 3(37.5%) were boys.4(50%) patients were below two years of age and 4(50%) were above 10 years of age. Children less than 2years presented with neurological symptoms (75%) in the form of regression of milestones and convulsions.one patient had cerebral atrophy on neuroimaging. Children more than ten years of age mainly presented with gastrointestinal symptoms in the form of vomiting and icterus. Two of them had bilious vomiting without a surgical cause. On investigations, five patients had pancytopenia of which three had given consented for bone marrow aspiration which was suggestive of megaloblastic anaemia. (Fig.1/2) All patients were treated with injectable vitaminB12 daily, then alternate day and then monthly with promising results. (Table1)

DISCUSSION

Vitamin B12 is important for DNA synthesis, formation and maintenance of myelin sheaths, the synthesis of neurotransmitters, and erythropoiesis. Clinical vitamin B12 deficiency has two main manifestations: haematological and neuropsychiatric disorders. [3]

Dietary absorption of vitamin B12 is a complex process that begins with haptocorrin (also known as transcobalamin I or R-binder) production by the salivary glands. When food is digested in the stomach by gastric acid and pepsin, free vitamin B12 is released. It binds to haptocorrin and is transferred to the intrinsic factor (IF) in the intestinal lumen by means of a pH dependent process. In the terminal ileum, the IF-B12 complex binds to IF receptors on the membrane surface of enterocytes and is then transferred through the ileal membrane. Vitamin B12 is subsequently released in the enterocytes and transferred to transcobalamin II (TC). The B12-TC complex–known as holotranscobalamin (holoTC)–arrives in the blood circulation and circulates.Then it is taken up by the cells. A maximum of 30% of circulating B12 is bound to TC, which represents metabolically active B12. The vitamin B12 that is bound to haptocorrin is thought to transport the surplus of vitamin B12 to the liver. [3]

Simultaneously, gastric parietal cells secrete intrinsic factor, which cannot interact with the vitamin B12-haptocorrin complex. Not until food moves into the duodenum, where trypsin and other pancreatic enzymes cleave haptocorrin, is vitamin B12 free to bind to intrinsic factor. Theresultant vitamin B12-intrinsic factor complex binds to the cubam receptor on the mucosal surface of enterocytes in the ileum.Vitamin B12 is then transported into the circulation by multidrug resistance protein 1, where it is readily bound by its transport protein transcobalamin II.

The vitamin B12-transcobalamin complex then binds to the transcobalamin receptors on hematopoietic stem cells (and other cell types), allowing uptake of the complex, with subsequent lysosomal degradation of transcobalamin. Free vitamin B12 is then available for cellular metabolism.

Nearly every step of this pathway can be disrupted in various pathologic states, but lack of intrinsic factor secondary to pernicious anaemia is the cause of vitamin B12 deficiency in most cases. Vitamin B12 is synthesized exclusively in micro-organisms, and in humans it is an essential component in methyl group transfer and cell division. The vitamin is crucially involved in the proliferation, maturation, and regeneration of neural cells. In combination with folic acid, as an enzymatic essential cofactor in the metabolism of homocysteine, vitamin B12 maintains low homocysteine levels [3].

A lowered serum holoTC concentration is the earliest marker of vitamin B12 deficiency and signals that the body does not have sufficient available vitamin B12 and that the B12 stores are emptying as a result of the negative balance of B12.Thus,

- Clinically inconspicuous vitamin B12 deficiency that has not been confirmed with a laboratory test is common in the general population. Clinical manifestations of B12 deficiency range from early neurological symptoms to haematological symptoms.
- Holotranscobalamin (holoTC) and methyl malonic acid (MMA) have higher sensitivity and specificity, compared with vitamin B12 determination and are regarded as modern biomarkers of B12 status. Total vitamin B12 as a marker results in underestimation of the prevalence of B12 deficiency.
- Early diagnosis of vitamin B12 deficiency is advisable because neurological symptoms may be irreversible and often occur before or without hematological manifestations.
- Patients with neurological symptoms of unknown etiology should

be tested for B12 deficiency and malabsorption. Hypotonia, neurodevelopmental retardation, seizures and tremors can be the presenting feature in infants[4,8,10]. Vitamin B12 deficiency can lead to cerebral atrophy and thinning of corpus callosum and delayed myelinisation in cranial MRI[5,6,8].Dyskinesia, microcephaly and language delay may also be the presenting feature[8].Other clinical features of vitamin B12 deficiency includes failure to thrive and lethargy[9]. A low intake of vitamin B12, malabsorption, pernicious anemia, and gastrointestinal disorders with a shift in pH should be considered in the diagnosis and treatment of vitamin B12 deficiency.

CONCLUSION

Our case series showed that megaloblastic anaemia is common in very young children as well as early adolescents. In very young infants, we highlight the importance of vitamin B12 supplementation to the mothers during pregnancy and lactation, especially the mothers who are vegans or lactovegetarians. In young infants with rapid brain growth, deficiency of vitamin B12 leads to irreversible brain damage and cerebral atrophy. Hence, the importance of early diagnosis of megaloblastic anaemia in patients of anaemia, as it is a preventable cause of irreversible brain damage.

Deficiency of vitamin B12 can lead to severe anaemia in older children as well, especially vegans. It remains an important cause of pancytopenia and jaundice.

Recommendation

Delay in diagnosis causes irreversible neurological damage. Hence, early diagnosis and treatment is recommended.

REFERENCES

1. Socha DS, DeSouza SI, Flagg A, Sekeres M, Rogers HJ. Severe megaloblastic anemia: Vitamin deficiency and other causes. Cleve Clin J Med. 2020 Mar;87(3):153-164. doi: 10.3949/ccjm.87a.19072. PMID: 32127439.
2. Sachdev HPS, Shah D.Vitamin B12(cobalamin) In: Nelsons textbook of paediatrics. 21st ed. Kliegman RM, Stanton BF, Geme JW,Schor NF. Elsevier, first south Asia ed,2017,vol1 chap 49.7, 328-329.
3. Herrmann W, Obeid R. Causes and early diagnosis of vitamin B12 deficiency. Dtsch Arztebl Int. 2008 Oct;105(40):680-5. doi: 10.3238/arztebl.2008.0680. Epub 2008 Oct 3. PMID: 19623286; PMCID: PMC2696961.
4. Incecik F, Hergüner MO, Altunbaşak S, Leblebisatan G.Turk J Pediatr Neurologic findings of nutritional vitamin B12 deficiency in children Jan-Feb 2010;52(1):1
5. Briani C, Dalla Torre C, Citton V, Manara R, Pompanin S, Binotto G, Adami F. Cobalamin deficiency: clinical picture and radiological findings. Nutrients. 2013 Nov 15;5(11):4521-39. doi: 10.3390/nu5114521. PMID: 24248213; PMCID: PMC3847746.October 2014
6. Acıpayam C, Güneş H, Güngör O, İpek S, Sarışık N, Demir NŞ. Cerebral atrophy in 21 hypotonic infants with severe vitamin B12 deficiency. J Paediatr Child Health. 2020 May;56(5):751-756. doi: 10.1111/jpc.14733. Epub 2019 Dec 23. PMID: 31868292.
7. Rizzo G, Laganà AS, Rapisarda AM, et al. Vitamin B12 among Vegetarians: Status, Assessment and Supplementation. *Nutrients*. 2016;8(12):767. Published 2016 Nov 29. doi:10.3390/nu8120767
8. Smolka V, Bekárek V, Hlídková E, Bucil J, Mayerová D, Skopková Z, Adam T,et al Metabolic complications and neurologic manifestations of vitamin B12 deficiency in children of vegetarian mothers. Cas Lek Cesk. 2001 Nov 22;140(23):732-5. Czech. PMID: 11787236.
9. Chalouhi C, Faesch S, Anthoine-Milhomme MC, Fulla Y, Dulac O, Chéron G. Neurological consequences of vitamin B12 deficiency and its treatment. Pediatr Emerg Care. 2008 Aug;24(8):538-41. doi: 10.1097/PEC.0b013e318180ff32. PMID: 18708898.
10. Yoganathan S, Thomas MM, Mathai S, Ghosh U. Neuroregression as an initial manifestation in a toddler with acquired pernicious anaemia. BMJ Case Rep. 2015 Dec 17;2015:bcr2015213540. doi: 10.1136/bcr-2015-213540. PMID: 26678841; PMCID: PMC4691932.