AnnalsofClinicalandMedical Case Reports

CaseReport ISSN2639-8109|Volume10

MegaloblasticAnemia

DuttaTK

DepartmentofClinicalHematology,India

***Correspondingauthor:**

TarunKumarDutta,
DepartmentofClinicalHematology,India,
E-mail: tkduttajipmer@yahoo.co.uk

Received: 26 Jan 2023
Accepted: 21 Mar 2023
Published:29Mar2023
JShort Name:ACMCR

Citation:

DuttaTK,MegaloblasticAnemia.AnnClinMed Case Rep. 2023; V10(15): 1-5

1. Abstract

Folic acid and cobalamin are B-group vitamins that play an essential role in many cellular processes in the body. Deficiency in one or both of these vitamins causes megaloblastic anaemia.This is a disease characterized by the presence of megaloblasts. Megaloblasts occur when inhibition of DNA synthesis causes abnormalmaturationbetweenthenucleusandthecytoplasmofthecell. Megaloblastic anemia causes macrocytic anemia and intramedullary hemolysis.The most common causes are folate (vitamin B9) deficiency and cobalamin (vitamin B12) deficiency. Megaloblastic anemia can be diagnosed based on characteristic morphologic and laboratory findings.Therapy involves treating the underlying cause eg, with vitamin supplementation in cases of deficiency.

2. IntroductionandHistory

Nutritionalanemiasarethecommoncausesofanemiainanypopulation. Though iron deficiency anemia is the commonest cause, megaloblastic anemia due to folic acid or vitamin B12 deficiency must be considered as well.

3. Case Report

A50-year-oldladydoctorreportedtomewithsevereanemia(Hb 4gm/dl).Initiallyconsideredtobeduetoirondeficiencyanemia, non-responsetoirontreatment,raisedsuspicionofotherpossibil- ities. On further probing it was found she was a pure vegetarian; evenhardlytookmilk(whichisusuallyagoodsourceofVitamin B12). Blood peripheral smear showed macro-ovalocytes and hy- per segmented neutrophils. Serum cobalamin level was found to besignificantlylow.PatientwastreatedwithInjectioncobalamin 1000µgdailyforseveraldaysandherreticulocytecountroserapidlyandhemoglobinshotuprapidly.Herhemoglobinnormalized withinfourweeks.Megaloblasticanemiawasfirstdescribedby Addisonin1849.In1880,Ehrlichidentifiedthemasprecursorsof giantblood cells;thusnamedmegaloblastic anemia.

4. Definition

ThemegaloblasticanemiasaredisorderscausedbyimpairedDNA synthesis due to impaired DNAsynthesis because of deficiencies of vitamin B12 or folic acid.

PathogenesisofMegaloblasticAnemia

Megaloblasticsticanemiaresultsfromabnormalmaturationofhematopoietic cells due to impaired DNAsynthesis. The cobalamin (Cbl) and folic acid are two essential vitamins for DNA biosynthesis. All proliferating cells will exhibit megaloblastosis; In the hematopoietic system this results in abnormal nuclear maturation withnormalcytoplasmicmaturation,apoptosis,ineffectiveerythropoiesis, intramedullary hemolysis, pancytopenia and typical morphological abnormalities in the blood and marrow cells.

Aetiology

It is multifactorial and may result from dietary deficiency, impaired absorption, and transport or impaired utilization of these vitamins in DNA synthesis.

PrevalenceandCausative Factors

On analyzing the literature, it is found that dietary and pregnancy relatedfolatedeficiencyareprobablythemostcommoncausesof megaloblastic anemias.The frequency of pernicious anemia (PA) is 0.25 – 0.5 cases per 1000 persons in their seventh decade of life.However,frequencyofPAisreportedtobehigherinSweden, Denmark, and the United Kingdom (100-130 cases per100,000 population). In a study conducted in Hong Kong on 84 consecutive Chinese patients with megaloblastic anemia (48 males and 36 females), the median age at presentation was 67 years, and vitaminB12deficiencywasfoundinallcasesandnonehadfolate

deficiency.

CobalaminDeficiency

A. VitaminB12Deficiency

Vitamin B12 is produced by microorganisms and is found almost exclusively in foods of animal origin. Normal body stores of vitaminB12are3to5mg,andtherecommendedadultdailyintake is 6-9 µg. Causes of vitamin B12 deficiency are listed below. Di- etary deficiency of vitamin B12 occurs less frequently than folate deficiency because body stores can last for years owing to efficient enterohepatic recycling mechanisms.Although uncommon, dietary B12 deficiency can occur even in industrialized countries instrictvegansandvegetarians,orinbreastfedinfantsofmothers with vitamin B12 deficiency. 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 and binds to haptocorrin. Simultaneously, gastric parietal cells secrete intrinsic factor, which cannot interactwiththevitaminB12-haptocorrincomplex.Notuntilfood movesintotheduodenum,wheretrypsinandotherpancreaticenzymes cleave haptocorrin, is vitamin B12 free to bind to intrinsic factor.TheresultantvitaminB12-intrinsicfactorcomplexbindsto the cubam receptor on the mucosal surface of enterocytes in the ileum. From there, vitamin B12 is transported into the circulation bymultidrugresistanceprotein1,whereitisreadilyboundby its transport protein transcobalamin II. The vitamin B12-transcobalamin complex then binds to the transcobalamin receptors on hematopoieticstemcells(andothercelltypes),allowinguptakeof the complex, with subsequent lysosomal degradation of transcobalamin. Free vitamin B12 is then available for cellular metabolism.Nearlyeverystepofthispathwaycanbedisruptedinvarious pathologic states, but lack of intrinsic factor secondary to perniciousanemiaisthecauseofvitaminB12deficiencyinmostcases.

Chronic atrophic autoimmune gastritis is an autoimmune process directedspecificallyateithergastricparietalcellsorintrinsicfac- tor, or both. Parietal cell damage leads to reduced production of gastric acid and intrinsic factor, accompanied by a compensatory increase in serum gastrin levels. Decreased intrinsic factor leads to reduced absorption of dietary vitamin B12, resulting in pernicious anemia. Chronic atrophic autoimmune gastritis affects the bodyandfundusofthestomach,replacingnormaloxynticmucosa with atrophic-appearing mucosa, often with associated intestinal metaplasia.

B. CausesofVitaminB12DeficiencyCommonCauses(related to malabsorption)

Autoimmunegastritis(perniciousanemia)Celiacdisease,Inflammatory bowel disease Surgical gastrectomy gastric bypass ileal resection.

C. LessCommonCauses

Nutritional (strict vegans, breastfed infants of mothers with vitaminB12deficiency)DiphyllobothriumlatuminfectionPancreatic insufficiencyDrugeffect(metformin,protonpumpinhibitors)Inherited disorders affecting intrinsic factor Rare inherited disorder (eg, methylmalonic acidemia, transcobalamin II deficiency).

D. Physiologic Considerations

Animalproducts(meatanddairyproducts)areonlydietarysource of cobalamin for humans. The minimal daily requirement is 6µg/day to 9µg/day.Total body stores are 2-5 mg of cobalamin (Cbl), approximately half of which is in liver.

E. ClinicalFeaturesofCobalaminDeficiency

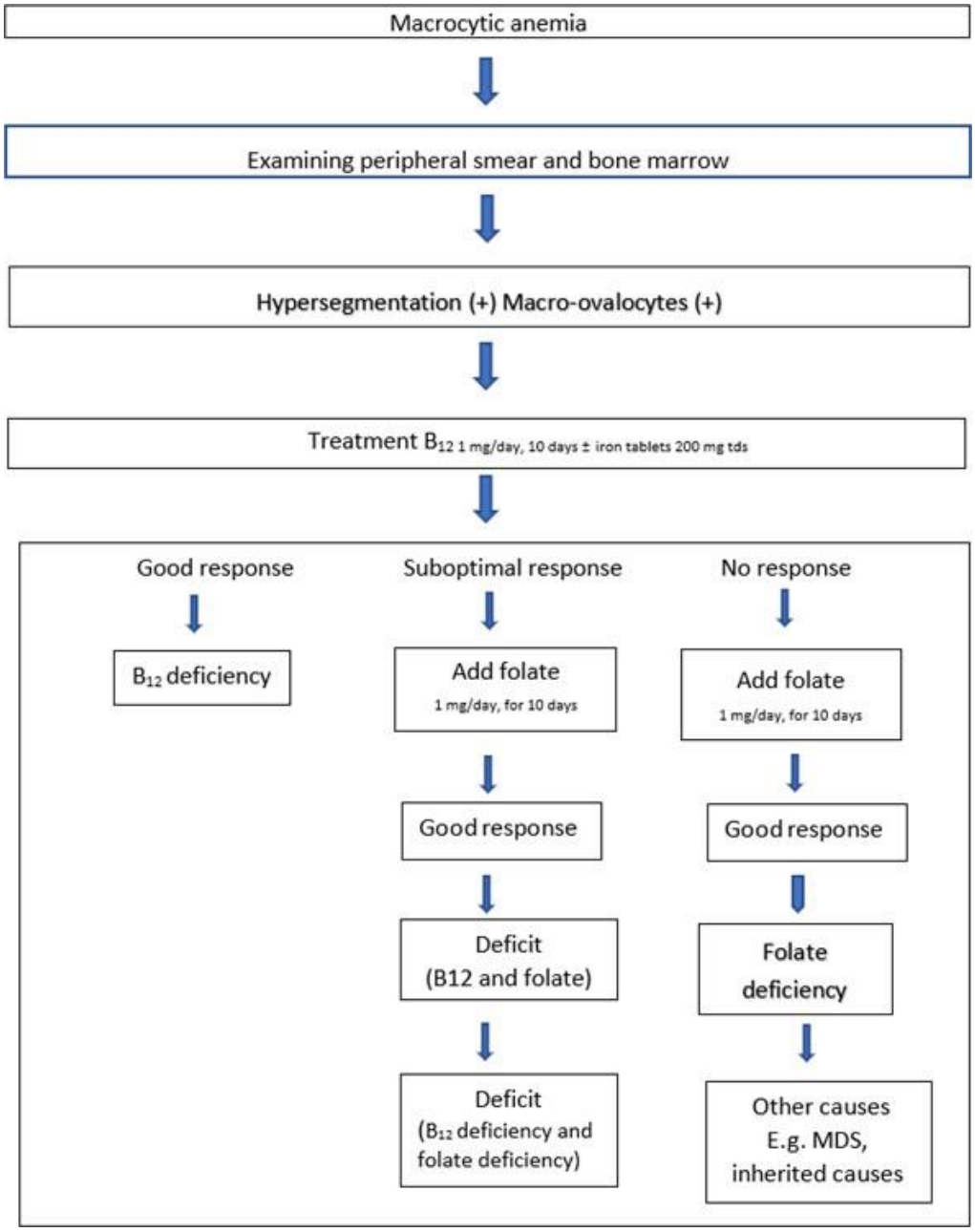
The classic picture of Cbl deficiency due to pernicious anemia is mentally sluggish person with a shiny tongue (atropic glossitis) andashufflingbroadgait.Thisclassicpictureisnowreplacedby more subtle presentation. Because cobalamin is required for all rapidlygrowingcells,includingentericmucosalcellsandepitheli- al cellsof skin,patients withcobalamin deficiencymay complain of glossitis, vaginal atrophy and malabsorption; they often have diffusehyperpigmentation,particularlyincreasedovertheknuckles.The patients may have neuro-psychiatric problems consisting of paresthesia, numbness, weakness, impaired memory and personality changes.

When the anemia is severe, there may be thrombocytopenia and neutropenia (i.e. pancytopenia).

F. NeurologicAbnormalities

NeuropsychiatricfeaturesVitaminB12deficiencycancausesubacute combined degeneration of the dorsal and lateral columns of thespinalcord.Patientsmayexperiencebilateralandsymmetrical paresthesia.Subacutecombineddegenerationofspinalcordisthe characteristic abnormality resulting from demyelination of dorsal andlateralcolumns.ThislesionisspecificforCbldeficiency.The neuropathy is symmetrical,affectingthe legs more than the arms. It begins with paresthesia and ataxia associated with loss of vibration and position and progress to severe weakness, spasticity, clonus and paraplegia. Other neurologic abnormaities that can be seen are axonal degeneration of peripheral nerves.Other symptomsincludememoryloss,irritabilityanddementia.Patientsmay presentwithLhermitte'ssyndrome,ashock-likesensationthatradiates to the feet during neck flexion.

Itisimportanttonotethatpatientswithneurologicmanifestations due to Cbl deficiency may not necessarily be anemic or may not even show macrocytic red cell indices.



Algorithm: Algorithmic approach for a tentative diagnosis

FolicAcidDeficiency

A. Physiologic Considerations

Folate occurs in animal products and leafy vegetables in the polyglutamate form. Normal daily requirement is about 200-400 µg/day;inpregnancyandlactation,thisincreasesto500-800µg/day. The most common cause of folate deficiency is nutritional due to poordietand/oralcoholism.Bodystoresaresmall(5-10mg)and individuals on a folate deficiency can develop megaloblastosis within 4-5 months.

Folate at physiologic level enters cells by binding to a folate receptor. Once inside the cell, folic acid is polyglutamated which is biologically active.

B. CausesofFolateDeficiency

- Alcohol abuse
- Pregnancy
- Hemolytic anemia
- exfoliative skin diseases
- drugse.g.phenytoin,trimethoprimmethotrexate
- malabsortion syndrome

C. Clinical Features

The hematologic manifestations are same as for cobalamin deficiency,butneurologicabnormalitiesdonotoccur.Anotherimpor- tant difference is the time gap for deficiency to develop. Because Cblstoresaresolargeininrelationtodailyintake,ayearofinadequateintakeisrequiredbeforeonsetofsymptomsoccurs.Onthe otherhand,symptomsoffolatedeficiencycanoccurwithinafew

weeksafterintakeisdiminished.Olderindividualswholivealone andavoidcookingfoodsthatcontainfolatemaybecomedeficient. Increased folate demands occur in pregnancy.

BothCblandfolicacidarerequiredformetabolismofhomocyst- eine to methionine.As a result, deficiencies in these vitamins can lead to increased plasma level of homocysteine and this is a risk factor for developing atherosclerosis and venous thrombosis.

D. Diagnosis

1. Anemia
2. RBCindex- MCV- >100 fl
3. Peripheral blood smear examination – macro-ovalocyte, hypersegmented neutrophil
4. Bonemarrowexamination-intenseerythroidhyperpla- sia, megaloblastic change, hypercellularity of marrow
5. SerumCbl - <200 pg/ml (N>300 pg/ml)
6. Serumfolate – <4ng/ml (N4ng/ml)
7. Specificmetabolites:Serummethylmalonatelevel (N-0.07-0.27µmol/l) and serum homocysteine level (N 5-15 µmol/l)

a. Cbldeficiency-Bothareelevated

b. Folatedeficiency–onlyhomocyteineelevated,methyl malonate (MMA) normal

ClinicalFeaturesin Common

A. MegaloblasticAnemias

1. Symptomsofanemia
2. SymptomsassociatedwithvitaminB12orFolicacidde- ficiencyNeurologicmanifestations(exclusivlywithB12 deficiency)
3. Gastrointestinal complaints (vit.B12 and folic acid de- ficiency), loss of appetite glossitis (red, sore, smooth tongue), diarrhea

Investigations

A. MegaloblasticAnemias- Diagnosis

1. Blood cell count: macrocytic anemia (MCV>100fl), thrombocytopenia, leucopenia (granulocytopenia), low reticulocyte count
2. Blood smear: macro-ovalocytosis, anisocytosis, poikilo- cytosis, hypersegmentation of granulocytes
3. Laboratory features: indirect hyperbilirubinemia, eleva- tionoflactatedehydrogenase(LDH),serumironconcen- tration- normal or increased
4. Bone marrow:
   - smear hypercellular
   - increased erythroid /myeloid ratio
   - erythroidcellchanges(megaloblasts,RBCprecursor - abnormally large with nuclear- cytoplasmic asyn- chrony)
   - myeloid cell changes (giant bands and metamyelo- cytes, hypersegmentation)
   - megakaryocytes are decreased and show abnormal morphology10

B. PerniciousAnemiaDiagnosis

1. Establishingvit.B12deficiencyanemia
2. Absence of hydrogen ion secretion (achlorhydria) with maximal histamine stimulation
3. Radiolabeled vitamin B12 absorption test (Schilling urinary excretion test): very reduced absorption of the B12-isotope,correctedtonormalonlywhenco-adminis- tered with a source of gastric IF
4. Intrinsic factor, parietal cell and IF-vit.B12 complex an- tibodies13

C. FolicAcidDeficiencyAnemiaDiagnosis

1. Establishing megaloblastic anemia
2. History:causesoffolatedeficiency
3. Absence of neurologic symptoms
4. Lowserum and red bloodcell folic acid level

MegaloblasticAnemiasManagement

A. TreatmentofCobalaminDeficiency

SevereanemiaistypicallytreatedwithparenteralCblinadoseas follows:

1000 µg (1 mg) daily x 7 days

Then1mgeveryweekx4weeks

Followed by 1 mg every month for rest of life.

Duringsevereanemia,ironsupplementationisrequiredbecauseof increased utilization of iron.

B. Laboratory Monitoring

If the patient is significantly anemic, there will be a rapid reticu- locytosis in 3-4 days, peaking at days 6 to 7 followed by a rise in hemoglobin and fall in MCV. Hemoglobin begins to rise within 10 days and returns to normal within 8 weeks. Hypersegmented neutrophilsdisappearat10-14days.Neurologicabnormalitiesim- prove about slowly over six months.

C. TreatmentofFolateDeficiency

Folate deficiency is treated with folic acid 1-5 mg /day for 1-4 months,oruntilcompletehematologicrecoveryoccurs.Adoseof 1 mg/day is usually sufficient.

Folic acid can partially reverse some of the hematologic abnor- malities of cobalamin deficiency, but the neurologic manifesta- tionswillprogress.Thus,itisimporttoruleoutCbldeficiency beforetreatingapatientofmegaloblasticanemiawithfolicacid.If

initiation of treatment is urgently required, blood samples should be obtained for appropriate assays ant the patient should be treated with both folic acid and vitamin B12 simultaneously until the results are known.

D. IndianScenarioofMegaloblasticAnemia

AstudyreportedthatT5%ofselectedurbanpopulationfromPune had a metabolic cause (hyperhomocsteinemia and hypermethylmalonicacidemia).Folatedeficiencyhasbeenlinkedtopoverty.In Delhi, a hospital based study showed that 2.7% of all anemia was megaloblastic anemia.

In another study from Puducherry, megaloblastic anemia was found in 38.4% out of 60 adult patients of macrocytic anemia-There was a significant male preponderance in the study, and a majoriy were young. The megaloblastic anemias observed were due to either vitamin B12 deficiency (78.3%) or combined vitamin B12 deficiency and folic acid deficiency (21.7%). None had lonefolatedeficiency.Asignificantproportionofnon-vegetarians (73.9%) had megaloblastic anemia [1-5].

5. Conclusion

The pathological conditions associated with macrocytic anemia aremuchmorediversethanisoftenappreciatedandmacrocytosis is not to be equated with megaloblastosis, since there are varied conditionsassociatedwithnon-megaloblasticmacrocytosis.However, the presence of macroovalocytes and hypersegmented neutrophils in peripheral smear almost always goes with a diagnosis of megaloblastic anemia. Megaloblastic anemia still remains the mostimportantcauseofmacrocyticanemiainoursetting.Thediversity and complexity of factors leading to macrocytic anemia preclude a single or uniform method of investigation. The investigative pattern must be tailored to the individual patient, giving importance to the clinical presentation. In settings with limited laboratoryfacilities,atherapeutictrialofvitaminB12orfolicacid is useful in determining the specifi c vitamin defi ciency in megaloblastic anemia

References

1. Chudgar U. Megaloblasic anemia. IN: Shah SN (ed). API TEXTBOOKOFMedicine,8thedition.Mumbai:TheAssociationofPhysicians of India. 2008; Pg No: 798-802.
2. Dutta TK, Panigrahi AK. Megaloblastic anemia: prevalence and causativefactors.InAgarwalAK(ed).MedicineUpdate.Delhi:Association of Physicians of India. 2009; Pg No: 187-90.
3. UnnikrishnanV,DuttaTK,BadheBA.Clinico-aetiologicprofileofmacrocyticanemiaswithspecialreferencetomegaloblasticanemia.IndianJournalofHematology&BloodTransfusion.2008;24:155-165.
4. Dutta TK. Megaloblasic anemia. In: Munjal YP, SHARMA SK, Agarwal AK et al (eds) API Textbook of Medicine, 10th edition, Delhi. 2015; Pg No: 1268-1273.
5. Socha DS, DeSouza SI, FlaggA, Sekere M, Rogers HJ. ClevelandClinic Journal of Medicine. 2020; 87(3): 153-64.