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Nutritional Anemia Types and Management

Hawraa Ali Alaliwi[1], Ghufran Abdulrahman Abukashba[2], Hussain Musa Alhussain[3], Mohammad HamdinAlhasnani[4], Saleh Hasan Alzahrani[4], Walaa Saleh Alharthi[5], Ali Ibrahim Sabei[6], Ahmed HeshamAlsharhan[7], Wejdan Hassan Bagadood[2], Sarah Ali Bunajimah[8], Mohannad M. Alshaya[9], Roba Mohammed Hamdan[10], Reem Moteb Alanazi[10], Sara Ahmad Najmi[11], Ismail Nizar Kraiz[1], Rakan Ahmed Alshuwaier[1]

1 King Saud University, 2 Ibn Sina National College, 3 Imam Abdulrahman Bin Faisal University, 4 Umm Alqura University, 5 King Abdulaziz University Hospital, 6 King Abdulaziz University, 7 Imam Muhammad Ibn Saud University, 8 Almaarefa Colleges, 9 King Saud Chest Hospital, 10 Arabian Gulf University, 11 Jazan University

Corresponding Author: HawraaAli Alaliwi- Dr.Hawraa-Alaliwi@Hotmail.Com - 0564555765

ABSTRACT

Background: Nutritional anemia or anemia due to dietary causes is the most common form, yet, it is the easiest to manage compared to other forms of anemia. Some of the most common nutritional deficiencies are iron, cobalamin, folate, and also other elements like copper. Anemia due to diet is mostly asymptomatic in the initial phase until the stores are depleted, which can take a few months to several years, depending upon the cause.
Methodology: We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE fromJanuary 1987 toMarch 2017. The following search terms were used: nutritional anemia, dietary anemia, iron deficiency anemia, cobalamin deficiency, folic acid deficiency anemia, dietary anemia treatment
Aim of the work: In this study we aimed at understanding the different types of anemia caused as a result of dietary deficiency. We also briefly studied their presentation, pathophysiology, and treatment.
Conclusion: Various causes of anemia, presentations, and complications associated with the different types of nutritional anemia, which is considered the easiest to treat and manage. Most cases are due to an underlying occult disorder rather than simple dietary insufficiency. Diagnosis can be more difficult in some cases, and require thorough history and investigations and integration to reach to an accurate conclusion and consequently treat the underlying cause.

Keywords: dietary anemia, iron deficiency anemia, cobalamin deficiency, folic acid deficiency anemia, dietary anemia treatment, nutritional anemia.

INTRODUCTION

Among many hematological diseases, nutritional anemia is considered the easiest to manage and treat. In contrast to other anemia which could be corrected when enough vitamins and minerals – required are supplemented for erythropoiesis. Whereas, other types of anemia depend mostly on other strategies oriented towards their pathophysiology. The prevalence of nutritional anemia is much less than other asymptomatic nutritional insufficiencies in the general population. A huge debate is raised about the necessity of treatment in mild cases if no other threat is present [1].

In this paper, we discussed these cases of asymptomatic nutritional insufficiencies with no symptom of anemia, and reviewed present data provided through the medical literatures. Nutrients which are required at relatively higher quantity, major acute loss, or low body stores are more likely to progress into symptomatic anemia. Otherwise, these deficiencies may take years before developing clinical features, which makes it easier to be reversed either spontaneously or by intervention[2].

METHODOLOGY

- Data Sources and search terms

We conducted this review using a comprehensive search of MEDLINE, PubMed and EMBASEfrom January 1987 to March 2017. The following search terms were used: nutritional anemia, dietary anemia, iron deficiency anemia, cobalamin deficiency, folic acid deficiency anemia, dietary anemia treatment

- **Data extraction**

Two reviewers have independently reviewed the studies, abstracted data and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

The study was done after approval of ethical board of King Abdulaziz university.

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Anemia due to dietary and non-dietary causes

An important distinction that mostly missed in our surveys was the distinction between diminished stores of a certain nutrient, and the presence of clinical signs and symptoms associated with this shortage.

People who have asymptomatic deficiency of a nutrient are far away than people who really suffer from clinical symptoms. National Health and Nutrition Examination Survey (NHANES) data, which was collected between 1991 and 1998, showed that nutritional anemia constitutes up to 34% of anemia in elderly. Other small studies found smaller rates ranging between 15-28%. This variation between results may be due to vitamin B12-deficiency, and folate-deficiency anemia which were detected more in the collected data [3].

The disadvantage of using population data is the inability of obtaining reliable diagnoses on individuals' levels, thus the inability to associate these abnormal results with clinical presentation or pathophysiology. This limitation of databases sometimes may cause the association between a certain nutritional deficiency and an irrelevant anemic case. Another limitation is the analysis of only nutritional problems, with neglecting other causes [4].

Iron-deficiency anemia

The most commonly encountered cause of nutritional anemia is iron-deficiency anemia, which is mostly found in infants and middle-aged women[5].

Pathophysiology

Iron is an essential part of hemoglobin, myoglobin, cytochrome, and peroxidases due to its role in the structure of heme; hemoglobin stores about 1.5-2.5 g of iron. Iron absorption occurs in the duodenum and is regulated strictly to avoid toxic iron accumulation, or deficiency. Oxidation and reduction reactions are necessary for iron to be absorbed, transported, and metabolized. One of important molecules that regulate iron is Hepcidin[5].

The daily need of an adult is about 1 mg of iron (0.179 mmol), which is satisfied by the daily intake of iron salts and heme summing up to about 10-20 mg iron. The type of food (meat as an example) is an important factor affecting the bioavailability of iron, thus iron serum levels. Other factors include promoters (acidity increases iron absorption), or inhibitors (like tea). The intake of less food will cause a decrease in iron, leaving premenopausal women at a high liability to develop deficiency[6].

The regulation of iron absorption 'also known as mucosal intelligence' is still an understood mechanism. The rate of absorption ranges between 1 to 20% of ingested iron, as this rate is influenced by the body's needs of iron for erythropoiesis. Normally in males, body contains about 1 g iron, mostly stored as ferritin-bound iron. The stores in females are less than males, and are about 300 mg. These stores provide spare iron for use in unstable states. When these stores are exhausted, hemoglobin synthesis will be negatively affected, marking the transition from asymptomatic iron deficiency, to iron deficiency anemia[7].

Diagnosis

Many tests for body's iron levels are available. However, the diagnosis of iron deficiency anemia is still somehow complicated as most of these tests have disadvantages. In iron deficiency anemia, the first noted change is serum ferritin levels decline, which can also be detected by hemosiderin staining in bone marrow. When ferritin levels become less than 12 ug/L, the diagnosis of iron depletion is made. However, in some inflammatory and chronic cases, the levels of ferritin may be falsely elevated, making this test alone insufficient for diagnosis. Moreover, during normal aging process, there may be continuous low-grade chronic inflammation ongoing, causing an increased levels of ferritin. For this reason, symptoms of iron deficiency appear on elderly when ferritin is on higher levels as 45 ug/L[8].

When iron levels are exhausted, the delivery of iron to cells decreases and transferrin levels increase as an attempt to increase levels. This will cause cells to synthesize TfR, which is also increased in any case of hematopoietic proliferation. This elevation of TfR is specific for iron deficiency anemia, and is reliable for distinguishing it from other causes as anemia of chronic disease[9].

When iron levels decrease, this will affect erythropoiesis, causing accumulation of protoporphyrin IX (heme precursor) in RBCs. However, measuring protoporphyrin IX levels is not reliable for making the diagnosis as it can accumulate due to other causes. In almost all the cases, all these tests must be done and analyzed in order to come with an accurate specific diagnosis. When a case of anemia responds to iron treatment, this provides a definitive diagnosis of iron-deficiency anemia. Rare

manifestations of iron deficiency anemia include cheilosis, koilonychia, PICA, and Plummer-Vinson syndrome. In children, iron deficiency anemia may be associated with cognitive decline, but this is not observed in adults[10].

Causes

Many etiologies can cause iron deficiency leading to anemia, most likely in children and premenopausal women. A significant cause of iron deficiency anemia is chronic blood loss. The cause of chronic blood loss in men and postmenopausal women is most likely in the gastrointestinal tract, which will need thorough examination of it to detect the bleeding. The cause of this loss is benign (as hemorrhoids) in most cases, but still there are major fatal causes of chronic blood loss, as cancers, vascular lesions, or drugs. Another cause of chronic bleeding is ancylostoma duodenale (also called hookworm) which is prevalent in tropical and subtropical areas, mainly in poor crowded areas. Infection with hookworm is usually associated with other diseases and problems as malnutrition. The severity of symptoms will here depend on the burden of worm infection and the general nutritional state. Hookworm most commonly affects children[11].

Blood loss from other places rather than the gastrointestinal tract is less common. This may occur after continuous phlebotomy, blood donation, hematuria, or pulmonary hemosiderosis. In cases of intravascular hemolysis, RBCs iron levels normally remains normal. When a source of blood loss cannot be determined, other causes must be taken in consideration. These include defects in iron absorption or bioavailability. An example of this is atrophic gastritis, which causes a decrease in stomach acidity, leading to decrease in iron absorption. Up to 48% of elderly can suffer from gastritis, and this can be autoimmune, drug-induced, or inflammatory. An important association with iron deficiency anemia is gastritis due to *Helicobacter pylori.* However, the association between H pylori and iron deficiency anemia still requires more studies to be confirmed or rejected. Post-gastrectomy can also be associated with iron deficiency anemia, together with vitamin B12 deficiency anemia. Iron malabsorption may also occur with lesions affection the duodenum, with inflammatory bowel diseases, and with celiac disease[12; 13].

Treatment and fortification

Within eight weeks of oral iron therapy, blood counts usually come back to normal levels. However, treatment is recommended to continue for months to restore body's irons stores, and to decrease the rate of anemia recurrence. In severe cases, continued loss, malabsorption, or noncompliance, IV iron can be used. The underlying cause of iron deficiency should also be treated[14].

In vulnerable populations, iron supplementation and fortification is recommended. However, the efficacy of this intervention may vary among individuals as the bioavailability of iron can be different due to several factors as daily food, gastritis, drugs, or other causes.When there is iron deficiency that is likely to progress, supplements are highly advised, with uncertain outcomes. The main concern when giving supplement is the risk of iron toxicity. In the United States, breakfast cereals provide iron fortification that is almost always above recommended values, causing supplements usually to be useless[15].

Cobalamin-deficiency anemia

Vitamin B12 deficiency is another important cause of nutritional anemia that affects elderly. Most cases are due to malabsorption (pernicious anemia). Any cause of vitamin B12 deficiency must persist for years before producing any symptoms, as the body stores are large. Rarely, vitamin B12 deficiency can be due to decreased dietary intake[16].

Pathophysiology

Vitamin B12 is essential in human for two pathways: the methylation of homocysteine, and the metabolism of propionate. Vitamin B12 can come only from animals products (as eggs), and its daily requirements is about 1 ug in adults. Normal adults have stores about 2,500 ug, making insufficiency during to dietary intake very rare. It is recommended that an adults consumes 2.4 ug daily of vitamin B12. Intrinsic factor is crucial for vitamin B12 absorption, and causes absorption in the ileum[17].

Diagnosis

When serum vitamin B12 levels become less than 200 ng, a diagnosis of deficiency is made. However, about 30% of cases provide false positive results. Therefore, the diagnosis must be consistent with blood counts and other clinical features. Other tests that may be useful include homocysteine, methylmalonic acid (MMA), or holo-TC II. This is most important with patients with no clinical features but B12 low levels. Although not highly specific, MMA testing is one of

the best tests for diagnosis. Homocysteine, Holo-TC II are not reliable for diagnosis due to unconfirmed specificity. No gold standard diagnostic test exists[16].

Clinical sequelae

Megaloblastic anemia is the result of significant vitamin B12 deficiency, with elevation of MCV. About 7% of patients do not have obvious macrocytosis, due to coexisting microcytic anemia. One of the early and specific signs for diagnosis is the presence of neutrophils hypersegmentation. Severe anemia can result later to pancytopenia if not managed properly. Other than anemia, manifestations of vitamin B12 deficiency include CNS dysfunctions, with about 6% of cases who will have persistent neurological symptoms even after treatment. Sometimes, patients are falsely diagnosed with folic acid deficiency instead of vitamin B12 deficiency and therefore given folic acid as a treatment. These patients' anemia may be masked due to the treatment, but neurological symptoms will progress. Therefore, it is recommended to avoid folic acid administration until vitamin B12 deficiency is ruled out[18].

Causes

A gastrointestinal disease is the cause of vitamin B12 anemia until proven otherwise. About 94% of causes are due to either gastric or ileal intrinsic factor mediated malabsorption. Pernicious anemia accounts for about 76% of anemia in elderly. Other causes include small bowel disorders (14%), or gastric surgery (3%). Making a diagnosis of these cases can be difficult sometimes due to the availability of intrinsic factor's antibodies test only, which is sometimes insensitive. Only 1% of clinical anemia is caused by nutritional deficiency, despite worldwide increasing prevalence of vegetarianism[19].

Treatment

Within eight weeks of treatment vitamin B12 injections, anemia usually resolves. In cases of malabsorption, injection should be given periodically to prevent recurrence. Patients with irreversible causes of malabsorption will need life-time therapy[20].

Folate-deficiency Anemia

Due to regulated and systematic fortification and supplementation of folic acid in the United States, Canada, and other countries, anemia due to folic acid deficiency has become relatively rare .This systematic approach actually targeted neural tube defects initially, but eventually it resulted in a significant decrease in folic acid deficiency and its related anemia. Folic acid usually has high bioavailability, with rare cases of malabsorption [21].

Pathophysiology

Almost all food types include folate, which is later reduced into folic acid to be absorbed and used. Non-reduced folic acid is relatively more stable and can be used in supplementation. Absorption of folic acid occurs in upper small intestine and has a bioavailability of about 50%. Normal adults are advised to take 400 ug daily. Folic acid is essential for the body and provides one-carbon unit for reactions. Folic acid stores constitute about 100-fold the daily requirements and loses. Folic acid deficiency can happen faster and in shorter periods than vitamin B 12 deficiency. However, as folic acid is present in many food types, cessation of one food type is very unlikely to cause deficiency, and deficiency needs severs malnutrition from different kinds of food, and usually occurs with deficiencies of other nutrients[22].

Diagnosis

The most important test in the diagnosis of folic acid deficiency is the detection of folate assays. However, this test still has its limitations, as sometimes its results are affected by even minor transient changes in intake. Another factor that affects diagnosis is the differences in deficiency definition. In most cases, a serum folate of less than 2.5 ug/L is considered deficient. However, some argue that suspect cases may have a cutoff of 5 ug/L[23].

On the other hand, RBCs folate levels do not change with transient changes thus can be used to reflect long-term status. However, this variant can lead to false positive results in cases of vitamin B12 deficiency, reticulocytosis, or hemolyzed blood samples. This inaccuracy led to significant limitations of RBCs folate levels use in diagnosis of folic acid deficiency anemia. Plasma homocysteine levels can be high in folic acid deficiency and may be used for diagnosis. However, this test is also nonspecific[24].

Folate-deficiency anemia

To diagnose folic acid deficiency, a combination of laboratory proof, clinical presentation, and an obvious cause should be provided. The reason of this is that vitamin B12 deficiency can produce megaloblastic anemia that is similar in presentation to folic acid deficiency anemia, and a wrong diagnosis will lead to improper management and long-term complications. The prevalence of folic acid deficiency anemia can vary from place to another and according

to the population, but in many cases, this deficiency is silent in nature and does not cause clinically appearing anemia. Therefore, routine screening of folic acid levels is not recommended. Moreover, it is also not recommended in cases of nonmacrocytic anemia. Only anemia with elevated MCV requires a diagnostic test for folic acid deficiency[25].

Folic acid fortification

The recent increase in use of vitamin supplementations (especially by older people), and the systematic fortification have significantly improved folate status and decreased the prevalence of folic acid deficiency. Mean levels of serum folate increased from 6.9 ug/L to 17.4 ug/L in 2000 in the United States. However, in 2004 there was a decrease in these levels of about 15.6 ug/L. The incidence of folic acid deficiency anemia has significantly decreased in the elderly and other age groups, and appears only in 0.1% of folate tests. Generally speaking, we can say that folic acid deficiency has disappeared in the developed world, prompting practitioners in these countries to stop screening for it. However, in developing countries, folic acid deficiency is still present and must be taken into consideration[26].

Treatment

Folic acid supplements are efficacious for treatment of deficiency, and they have a high bioavailability. This is not the case in vitamin B12 deficiency where oral supplementation does not cause good response. In cases of confirmed folic acid deficiency, alcoholism, malabsorption, or other causes must be taken into consideration, as normal and nutritional deficiency has become extremely rare after fortification. In severe cases, if normal oral therapy fails, higher doses can be tried. In case of failure, give folic acid injections. It is essential to rule out vitamin B12 deficiency before administrating folic acid as this will cause deterioration of neurological manifestations[27].

CONCLUSION

Different etiologies, presentations, and complications are associated with different types of nutritional anemia, but they still are the easiest to treat and manage. Most cases are due to an underlying occult disorder rather than simple dietary insufficiency, making diagnosis more difficult in some cases, and requiring thorough history and investigations integration to reach an accurate diagnosis and treat the underlying cause. MCV abnormalities can be an important measure to classify anemia, and rule out nutritional anemia (when normal). Microcytosis or macrocytosis are not enough alone for making a diagnosis, and can lead to false positive results especially in adults. Instead, the full clinical picture and investigations should be taking into consideration before making a diagnosis.

In order to make a diagnosis and manage accordingly, basic pathophysiology of anemia, their causes, and their treatments must be well understood.

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