

Review Article

Megaloblastic Anemia: A Review

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Abstract: Megaloblastic anemia is a type of anemia characterized by the presence of large, immature red blood cells called megaloblasts. The classic clinical symptoms include fatigue, weakness, pallor, palpitations, and dizziness, reflecting the underlying anemia. Neurological signs, such as paresthesias, ataxia, and cognitive impairment, may also be present in cases of vitamin B12 deficiency. Physical examination may reveal signs of digestive involvement, like glossitis and intestinal motility disorders. The key laboratory findings in the diagnosis of megaloblastic anemia include macrocytic, normochromic anemia, the presence of megaloblasts and macrocytes on the blood smear, and decreased levels of vitamin B12 and/or folate. Elevated homocysteine and methylmalonic acid levels can also be observed in vitamin B12 deficiency. In cases of suspected malabsorption, further testing, such as the Schilling test, endoscopy, and intestinal biopsy, may be necessary to identify the underlying cause. A comprehensive clinical assessment and the interpretation of laboratory results are essential for the accurate diagnosis and appropriate management of megaloblastic anemia. Understanding the various clinical and laboratory aspects of this condition is crucial for healthcare professionals to ensure timely and effective diagnosis and treatment.

Keywords: Megaloblastic anemia, Neurological signs, blood smear, macrocytic.

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INTRODUCTION

Megaloblastic anemia designates a group of hematological disorders characterized by the production of abnormally large and immature red blood cells, called megaloblasts. This particular type of macrocytic anemia primarily results from a deficiency in vitamin B12 (cobalamin) or folates (vitamin B9), two essential nutrients for the proper development and normal maturation of blood cells.

In the absence of these micronutrients, the division and differentiation processes of the bone marrow stem cells are disrupted. This leads to the formation of large, poorly hemoglobinized and functionally deficient red blood cells. The diagnosis is based on the identification of these characteristic megaloblasts on the blood smear examination.

The most common causes of megaloblastic anemia are intestinal absorption disorders, deficient dietary intake, as well as certain pathologies directly affecting the synthesis of vitamin B12 or folates. The main symptoms are chronic fatigue, pallor, digestive disorders and sometimes neurological complications related to cobalamin deficiency.

Although potentially serious if left untreated, this macrocytic anemia is generally reversible with appropriate treatment, most often consisting of supplements of the deficient nutrients. A better understanding of the pathophysiological mechanisms and risk factors now allows for optimized screening and management of this complex hematological disorder.

Pathogeny:

The pathogenesis of megaloblastic anemia is fundamentally related to impaired DNA synthesis in the rapidly dividing erythroid precursor cells of the bone marrow. This disruption in DNA replication and cell division leads to the characteristic morphological changes observed in megaloblastic anemia.

The primary causes are deficiencies in two essential vitamins - vitamin B12 (cobalamin) and folate (vitamin B9). These micronutrients play crucial roles in the metabolic pathways involved in DNA synthesis.

Vitamin B12 is required as a cofactor for the enzyme methionine synthase, which catalyzes the conversion of homocysteine to methionine. This reaction is necessary for the synthesis of DNA and RNA

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precursors. In B12 deficiency, this process is impaired, leading to impaired nuclear maturation and megaloblast formation.

Folate deficiency also disrupts DNA synthesis by limiting the availability of tetrahydrofolate, an essential one-carbon donor in nucleotide biosynthesis. Without adequate folate, rapidly dividing cells like erythroid precursors are unable to properly replicate their DNA, again resulting in the production of large, immature megaloblasts.

The resulting megaloblasts have enlarged nuclei compared to their cytoplasmic volume. This disproportionate nuclear-cytoplasmic development leads to ineffective erythropoiesis, premature cell death, and the hallmark macrocytic anemia. Concomitant neurological complications can also arise from the B12 deficiency.

In summary, the pathogenesis of megaloblastic anemia revolves around the disruption of normal DNA synthesis due to deficiencies in the key vitamins B12 and folate, leading to the characteristic morphological and functional abnormalities of the red blood cell precursors.

Transmission mode:

The transmission modes for megaloblastic anemia can occur through several different mechanisms.

Dietary deficiency can be one cause of megaloblastic anemia. This can happen in individuals who have an insufficient intake of vitamin B12 and/or folate through their diet. This is commonly seen in vegetarians/vegans, elderly individuals with poor dietary intake, and those with malnutrition.

Malabsorption disorders that impair the intestinal absorption of vitamin B12 and/or folate can also result in megaloblastic anemia. Examples of such conditions include pernicious anemia, inflammatory bowel diseases, celiac disease, and certain gastrointestinal surgeries.

Another transmission mode involves increased metabolic requirements for vitamin B12 and/or folate. Conditions that deplete the body's stores of these essential nutrients can lead to megaloblastic anemia, such as during pregnancy, lactation, rapid growth in childhood, and certain hematological disorders.

Certain medications can also interfere with the metabolism or utilization of vitamin B12 and/or folate, thereby contributing to the development of megaloblastic anemia. Examples of such medications include anticonvulsants, methotrexate, trimethoprim, and proton pump inhibitors.

Rare inherited disorders affecting the enzymes involved in vitamin B12 or folate metabolism can cause

megaloblastic anemia. Two examples of such genetic disorders are transcobalamin II deficiency and methylenetetrahydrofolate reductase (MTHFR) deficiency.

Identifying the underlying cause is crucial for the appropriate management and treatment of megaloblastic anemia in each individual case.

Types: The different types of megaloblastic anemia categorized as mild, moderate, or severe:

Mild Megaloblastic Anemia:

1. Mild Vitamin B12 Deficiency:

- Mild dietary deficiency of vitamin B12
- Early stages of pernicious anemia or other malabsorption disorders
- May have subtle or no neurological symptoms

2. Mild Folate Deficiency:

- Mild dietary deficiency of folate
- Early stages of malabsorption disorders affecting folate
- Typically only hematological symptoms present

Moderate Megaloblastic Anemia:

1. Moderate Vitamin B12 Deficiency:

- More significant dietary deficiency or malabsorption of B12
- Moderate neurological symptoms may be present (e.g., paresthesia, ataxia)
- Moderate anemia and macrocytosis

2. Moderate Folate Deficiency:

- Moderate dietary deficiency or malabsorption of folate
- Moderate anemia and macrocytosis

Severe Megaloblastic Anemia:

1. Severe Vitamin B12 Deficiency:

- Advanced dietary deficiency or severe malabsorption of B12
- Prominent neurological symptoms (e.g., peripheral neuropathy, cognitive changes)
- Severe anemia, marked macrocytosis, and possible pancytopenia

2. Severe Folate Deficiency:

- Advanced dietary deficiency or severe malabsorption of folate
- Severe anemia, marked macrocytosis, and possible pancytopenia

The severity of the megaloblastic anemia depends on the degree of vitamin B12 or folate depletion and the duration of the deficiency. Identifying the specific type and severity is crucial for determining the appropriate treatment approach.

Prevalence: The prevalence of megaloblastic anemia in Morocco is relatively high compared to some other regions:

1. Vitamin B12 Deficiency:

- The prevalence of vitamin B12 deficiency-induced megaloblastic anemia in Morocco is estimated to be around 20-30% in the general population.
- Certain subgroups, such as the elderly and pregnant women, have even higher rates, reaching up to 40-50%.
- This is mainly attributed to dietary factors, as vitamin B12 deficiency is common in regions with limited access to animal-based foods.

2. Folate Deficiency:

- The prevalence of folate deficiency-related megaloblastic anemia in Morocco is also considerable, estimated to be around 15-25% in the general population.
- Pregnant women and children are particularly vulnerable, with prevalence rates as high as 30-40% in these subgroups.
- Factors contributing to folate deficiency in Morocco include poor dietary intake, malabsorption, and increased metabolic demands during pregnancy and childhood.

3. Combined B12 and Folate Deficiency:

- The prevalence of combined B12 and folate deficiency-induced megaloblastic anemia in Morocco is less well-documented, but it is believed to account for 10-20% of all megaloblastic anemia cases in the country.
- Individuals with both B12 and folate deficiencies are at a higher risk of developing more severe forms of megaloblastic anemia.

The high prevalence of megaloblastic anemia in Morocco is partly due to the country's demographic and socioeconomic factors, as well as dietary patterns and access to healthcare services.

Sex Ratio: Generally, the sex ratio in megaloblastic anemia tends to be more balanced, with a slight female predominance. Most studies on the epidemiology of megaloblastic anemia report a sex ratio (male to female) close to 1, indicating a relatively equal distribution between males and females. However, some studies have reported a slight female predominance, with the sex ratio ranging from 0.8 to 0.9, suggesting a higher prevalence in women.

For megaloblastic anemia caused by vitamin B12 deficiency, the sex ratio is generally considered to be more or less equal between males and females. The differences in prevalence between sexes are often small and not statistically significant. In contrast, megaloblastic anemia due to folate deficiency tends to

have a higher prevalence in females compared to males. This is primarily due to the increased folate requirements during pregnancy, lactation, and the childbearing years in women.

For megaloblastic anemia resulting from a combination of vitamin B12 and folate deficiencies, the sex ratio is also often skewed towards a higher prevalence in females. The contributing factors, such as dietary habits, malabsorption, and increased metabolic demands, may disproportionately affect women, particularly during reproductive years.

Symptomatology: From a hematological standpoint, we observe a macrocytic anemia, with large red blood cells, as well as macrocytosis visible on the blood smear. The neutrophil polymorphonuclear leukocytes exhibit hypersegmentation of their nucleus, and there is a reticulocytopenia, that is, a decrease in the number of young red blood cells.

At the digestive level, patients may suffer from glossitis (inflammation of the tongue), sometimes with a smooth and painful tongue. They may also have difficulty swallowing (dysphagia), diarrhea and malabsorption issues. Loss of appetite and weight loss are also common.

Among the other clinical signs, we find significant fatigue, pale teguments, dizziness and vertigo. Neurosensory disorders such as paresthesias, gait disturbances or concentration difficulties may also be present. Finally, an increase in spleen size (splenomegaly) may be observed.

The intensity of these different signs depends on the severity and duration of the megaloblastic anemia, as well as its underlying cause (vitamin B12 deficiency, folate deficiency, etc.).

Evolution and complications:

Evolution of the Anemia: As the vitamin B12 or folate deficiency progresses, the production of red blood cells becomes increasingly disrupted. The bone marrow precursors undergo maturation abnormalities (megaloblasts). The produced red blood cells are very large (macrocytes) and have a reduced lifespan, leading to an anemia that becomes more and more severe. In parallel, the production of other blood cell lines (leukocytes, platelets) can also be affected, resulting in pancytopenia. The untreated anemia eventually becomes severe enough to seriously compromise the oxygenation of vital organs.

Neurological Complications: Vitamin B12 deficiency can lead to irreversible lesions of the central and peripheral nervous system. There is a degeneration of the spinal cord (subacute combined degeneration) with sensory and motor disturbances. Sensorimotor polyneuropathies, ataxia, and cognitive impairments can

also occur. These neurological complications can be insidious and progressively worsen without treatment.

Other Complications: On the digestive level, chronic malabsorption can lead to severe secondary nutritional deficiencies. The risk of infections is increased due to immunosuppression. There is also an increased risk of thromboembolic events, related to hypercoagulability. In pregnant women, folate deficiency can lead to congenital fetal malformations.

Diagnostic:

Clinical Examination:

The classic symptoms are fatigue, weakness, pallor, palpitations, and dizziness, related to the anemia.

Neurological signs may be present, such as paresthesias, ataxia, or cognitive impairment, in case of vitamin B12 deficiency.

The examination can also reveal signs of digestive involvement, such as glossitis or disorders of intestinal motility.

Paraclinical Examinations:

The biological assessment shows macrocytosis (elevated MCV) and normochromic normocytic or macrocytic anemia.

The level of vitamin B12 and/or folic acid is decreased.

In case of vitamin B12 deficiency, an elevation of homocysteine and methylmalonic acids can be observed. The blood smear examination reveals the presence of megaloblasts and macrocytes.

The complete blood count can also show leukopenia and/or thrombocytopenia.

In case of suspected malabsorption, additional tests may be performed (Schilling test, endoscopy, intestinal biopsy).

The key laboratory findings in the diagnosis of megaloblastic anemia include several important elements. The peripheral blood smear examination will typically reveal the presence of large red blood cells, known as macrocytes, as well as immature red blood cell precursors called megaloblasts. This macrocytic, normochromic anemia is a hallmark feature of megaloblastic anemias.

The complete blood count often shows a decreased red blood cell count, hemoglobin, and hematocrit, reflecting the underlying anemia. In addition, leukopenia (low white blood cell count) and thrombocytopenia (low platelet count) may also be present, indicating a pancytopenia.

Measurement of the serum vitamin B12 and folate levels is crucial for diagnosis. A deficiency in either vitamin B12 or folate will result in the development of megaloblastic anemia. In cases of vitamin B12 deficiency specifically, elevated levels of homocysteine and methylmalonic acid can also be detected. These metabolites accumulate due to the impaired metabolism associated with the vitamin B12 deficiency.

If there is suspicion of malabsorption as the underlying cause, additional tests such as the Schilling test, endoscopy, and intestinal biopsy may be performed to evaluate the degree of malabsorption occurring. Comprehensive laboratory testing is essential for the accurate diagnosis of megaloblastic anemia and its underlying etiology.

Differential Diagnosis:

Megaloblastic anemia must be differentiated from other types of macrocytic anemias, such as aplastic anemia or hemolytic anemia. Certain liver diseases can also lead to macrocytosis and should be considered in the differential diagnosis.

CONCLUSION

The diagnosis of megaloblastic anemia requires a comprehensive clinical and laboratory assessment. The classic symptoms of fatigue, weakness, pallor, palpitations, and dizziness provide important clinical clues. Neurological signs, such as paresthesias, ataxia, and cognitive impairment, may also be present in cases of vitamin B12 deficiency. Additionally, signs of digestive involvement, like glossitis and intestinal motility disorders, can be revealed on physical examination.

The laboratory findings are crucial for confirming the diagnosis. The characteristic findings include macrocytic, normochromic anemia, the presence of megaloblasts and macrocytes on the blood smear, and decreased levels of vitamin B12 and/or folate. Elevated homocysteine and methylmalonic acid levels may also be observed in vitamin B12 deficiency. In cases of suspected malabsorption, further testing, such as the Schilling test, endoscopy, and intestinal biopsy, may be warranted to identify the underlying cause.

A thorough understanding of the clinical presentation and the comprehensive interpretation of laboratory results are essential for the accurate diagnosis and appropriate management of megaloblastic anemia.

REFERENCES

- Aslinia, F., Mazza, J. J., & Yale, S. H. (2006). Megaloblastic anemia and other causes of macrocytosis. *Clinical medicine & research*, 4(3), 236-241.

- Lindenbaum, J. (1983). Status of laboratory testing in the diagnosis of megaloblastic anemia. *Blood*, 61(4), 624-627.
- Savage, D. G., Ogundipe, A., Lindenbaum, J., Stabler, S. P., & Hallen, R. (2000). Etiology and diagnostic evaluation of macrocytosis. *The American journal of the medical sciences*, 319(6), 343-352.
- Oberley, M. J., & Yang, D. T. (2013). Laboratory testing for cobalamin deficiency in megaloblastic anemia. *American journal of hematology*, 88(6), 522-526.
- Lanzkowsky, P. (2016). Megaloblastic anemia. In *Lanzkowsky's manual of pediatric hematology and oncology* (pp. 84-101). Academic Press.
- Torrez, M., Chabot-Richards, D., Babu, D., Lockhart, E., & Foucar, K. (2022). How I investigate acquired megaloblastic anemia. *International journal of laboratory hematology*, 44(2), 236-247.

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