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Anemia: A Global Health Challenge with Multifactorial Implications

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ABSTRACT

Anemia is the most prevalent hematologic disorder worldwide, affecting over one billion individuals. It is characterized by a reduction in hemoglobin levels, leading to tissue hypoxia and systemic complications. The condition is classified based on onset, pathophysiology, and mean corpuscular volume, with the latter being the most widely used parameter in clinical practice.

Iron deficiency remains the primary cause of anemia, followed by anemia of inflammation, particularly in high-risk populations such as children, pregnant women, and the elderly. In children, iron deficiency anemia is highly prevalent and has been linked to neurocognitive developmental delays. Among women, menstrual blood loss and pregnancy significantly contribute to iron depletion, affecting overall health and maternal-fetal outcomes. In the elderly, anemia often results from multifactorial causes, including chronic inflammation, nutritional deficiencies, and underlying diseases, leading to impaired cognitive and physical function.

Recent advances in anemia research have highlighted the role of inflammatory pathways, hepcidin regulation, and novel therapeutic strategies, such as targeted iron supplementation and erythropoiesis-stimulating agents. Addressing anemia requires a multidisciplinary approach, integrating early diagnosis, nutritional interventions, and individualized treatment strategies to mitigate complications and improve patients' quality of life.

Introduction

Anemia is the most common hematologic disorder in the world, affecting more than one billion people worldwide.[1] It is defined as a reduction in the amount of hemoglobin, which is essential for oxygen transport and, if deficient, can result in tissue hypoxia.[2,3] In addition, it can be classified in several ways: 1) acute and chronic, according to the time of onset; 2) resulting from decreased production (hypoproliferative) or increased destruction of erythrocytes (loss or hemolysis); 3) according to the cause; and 4) as normocytic, macrocytic, and microcytic, according to the mean corpuscular volume (MCV). In clinical practice, the most commonly used classification is according to the MCV, guiding the clinician in relation to the etiologies.[2]

Among the causes of anemia, the most prevalent is iron deficiency, followed by that resulting from inflammatory disease.[2] Iron deficiency anemia results from the depletion of iron stores, which has a multifactorial cause and is caused by chronic blood loss, such as increased menstrual flow and bleeding from the gastrointestinal tract.[2] Despite the multifactorial nature of the disease, dietary iron deficiency remains the leading cause of anemia in almost all regions, and nutritional interventions are essential.[4] Regarding anemia of inflammatory disease, it results from the blockage of iron in the reticuloendothelial system, reduced erythropoiesis, and shorter red blood cell survival. Ferritin is decreased in iron deficiency anemia and increased (or normal) in anemia of inflammatory disease. Other common types of anemia include anemia of pregnancy, anemia secondary to renal failure, and multifactorial anemia in the elderly.[2]

Anemia is a public health problem that is widespread in the world population, with the most affected groups being children, pregnant women, and the elderly.[1] The World Health Organization (WHO) estimates that approximately one-quarter of the world's population suffers from anemia, including almost half of preschool-age children. Globally, microcytic anemia is the most common hematologic disorder in children, and iron deficiency is the most common cause in this group.[5] However, there are other important causes of anemia in children: hemoglobinopathies, infections, and other chronic diseases. Early diagnosis is extremely important, since anemia is associated with increased morbidity, including neurological complications, increased risk of low birth weight, infection, and heart failure, as well as increased mortality. When approaching a child with anemia, detailed historical information, particularly diet, environmental exposures, and family history, often provide important clues to diagnosis. Dysmorphic features on physical examination may indicate syndromic causes of anemia.[6]

Normocytic anemia is classified by reticulocyte count and may reflect hemolysis (elevated reticulocyte count) or bone marrow suppression (low reticulocyte count). Macrocytic anemia is less common in children and usually results from nutritional deficiencies or malabsorption of cobalamin (vitamin B12) or folate.[5]

In women, iron deficiency anemia is more prevalent, and is primarily related to menstrual blood loss, abnormal uterine bleeding, and pregnancy.[7] These factors place women at risk for developing iron deficiency, which can result in chronic fatigue, cognitive impairment, and poor quality of life, reduced exercise capacity, and poor work performance. Furthermore, iron deficiency and anemia during pregnancy are associated with worse maternal and fetal outcomes.[8,9]

With the increase in average life expectancy, the elderly have become a significant risk group, since aging and the onset of anemia are expected to have an impact on their physical and cognitive performance and public health. The development of anemia in the elderly can have several causes due to the greater number of complications and comorbidities, making it more difficult to determine its etiology in most cases.[10] In this population group, anemia can be subdivided into 3 types: anemia due to nutritional deficiency (iron, vitamin B12 and/or folic acid), anemia associated with chronic/inflammatory diseases or anemia of less common causes, such as

myelodysplastic syndromes. Approximately one third of cases are deficiency anemias, due to inadequate nutrition, or arise due to blood loss from the gastrointestinal tract, with the most common cause of anemia being iron deficiency.[10] On the other hand, inflammatory conditions, cardiovascular diseases or chronic renal failure are frequently associated with anemia, contributing to the second leading cause in the elderly. And, finally, renal endocrine deficiencies, androgenic alterations or myelodysplastic syndromes also contribute to anemia.[10]

It is important not to underestimate or trivialize the disease, even when mild and mildly symptomatic, given that socioeconomic, intellectual and quality of life losses can result from this problem. Not to mention the increased mortality in biologically more fragile populations. It is essential to emphasize in medical training and in the education of the general population the importance of the subject, the impact that anemia has on quality of life, so that we can begin to seek better results. Knowledge is the first step to prevention and providing the best treatment.[11]

Methodology

This study is an integrative literature review that aims to understand why children, women of childbearing age, and the elderly are considered at risk for anemia. The searches were conducted using the PubMed Central (PMC) database, Scielo platform. The inclusion criteria were as follows: articles published in English or Portuguese, from 2001 to 2024, and that addressed the topics relevant to this research. The DeCS (health science descriptors) anemia, diagnosis, anemia in children, anemia in women, and anemia in the elderly were used. Articles published in the previous year of 2001 were excluded and articles whose language is not English and Portuguese.

CHILDREN

Anemia is the most prevalent hematologic abnormality identified in infants and children.[1] Globally, it affects up to half of the children under five years old.[12] This condition is associated with increased pediatric morbidity and mortality, especially in preschool-aged children. Additionally, anemia represents a heterogeneous group of pathological conditions. During the first year of life, erythrocytes lose their fetal and neonatal characteristics, undergoing significant changes reflected in decreases in hemoglobin levels, as well as MCV, mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). These hemoglobin levels progressively increase throughout childhood and eventually stabilize in adulthood. The diagnostic evaluation of anemic children should combine medical history, physical examination, and laboratory investigation. The patient's age should be considered, as different disorders are prevalent at different ages. Physical findings generally reflect the timing, severity, and type of anemia.[1]

Microcytic anemia due to iron deficiency is the most common type of anemia in children, while macrocytic anemia is rare in this age group.[12] Preschool-aged children constitute a particularly vulnerable group for iron deficiency anemia among at-risk populations, raising concern due to its associated impairments, such as immune system depression, reduced cognitive function, and compromised growth and psychomotor development. These changes may persist even after pharmacological treatment. Although various factors contribute to anemia, its high prevalence in childhood is believed to result from a combination of increased iron requirements due to rapid growth and development and diets that are generally low in heme iron.[13] Additionally, malaria is frequently identified as one of the leading causes of severe anemia, particularly in African children.[14]

Several studies have indicated that the typical characteristics of anemic children include being under 2 years old, male, having low birth weight, reduced birth length, prematurity, having multiple siblings, poor nutritional status (such as stunting,

wasting, or underweight), smaller head circumference, lack of exclusive breastfeeding, early introduction of complementary foods (before 6 months), use of formula milk, incomplete immunization, pale skin coloration, low maternal education, young maternal age, low-income families, and residence in rural areas.[15]

It is evident that low dietary intake and high prevalence of iron deficiency occur in both low- and high-income countries. Strategies for the prevention and control of anemia have been described, including improving dietary intake and increasing dietary diversity with a focus on iron bioavailability, targeted food fortification for high-risk groups (such as infant formulas), and iron (and folic acid) supplementation for these vulnerable populations. However, there are barriers to the dissemination and adoption of these programs, including insufficient prioritization, lack of knowledge and education about anemia prevention, and challenges in addressing the needs of high-risk groups at critical stages of life. Since the early years of life represent a critical period for mental and psychomotor development, anemia prevention should be continuously supported, encouraged, and implemented.[6]

Hereditary hemoglobin disorders, such as thalassemia, sickle cell anemia, and hemolytic anemias, represent the second most common cause of anemia worldwide, particularly in East Asia. Advances in the treatment of hemoglobin disorders have led to a reduction in mortality rates among affected children under 5 years old. Consequently, many children with thalassemia or sickle cell trait, who previously would not have survived childhood, are now living due to improved diagnosis and appropriate disease management.[6]

The incorporation of DNA sequencing methodologies has significantly improved the genetic diagnosis of hereditary anemias, enabling the precise identification of disease-causing mutations. Strategies such as targeted gene capture, gene panels, and exome sequencing have been widely used, allowing new mechanistic insights and the diagnosis of previously unidentified cases. However, challenges remain, including the detection of variants of uncertain significance and limitations in identifying distant regulatory mutations and deep intronic splicing mutations. Whole-genome sequencing, still primarily used in research, has shown potential for providing precise genetic diagnoses in complex cases.[16]

Recent scientific advancements have significantly improved our understanding of erythropoiesis and associated disorders, opening up new therapeutic opportunities. Key discoveries include identifying GDF11 as a negative regulator of erythropoiesis and recognizing various enzymes, cytokines, and hormones that regulate iron metabolism. Technological progress, such as refined lentiviral vectors and gene-editing tools, holds promise for alleviating or repairing genetic defects causing anemia. However, challenges remain in understanding the role of cytokines and the potential toxic effects on surrounding tissues, as well as the difficulty in manipulating newly identified transcriptional regulators like BCL11A and histone-modifying enzymes. Most current knowledge of human hematopoiesis is based on mouse models, which have limitations due to fundamental differences between species. New methods for studying human hematopoiesis are essential for developing effective therapies.[17]

While advanced approaches like gene therapy and biologic drug infusions are promising, they may not be feasible for large populations in developing countries, where conditions like sickle cell disease and β-thalassemia are prevalent. Therefore, there is a need for a balanced approach, focusing on advancing existing therapies such as hydroxyurea and developing affordable oral treatments. Basic interventions like regular transfusions and iron chelation also provide significant benefits for individuals with anemia. Ultimately, improving anemia treatment requires collaboration among scientists, clinicians, and researchers to deliver optimal therapies to those most in need, especially in regions heavily affected by anemia.[17]

WOMEN

Anemia and iron deficiency are global health problems and are the leading causes of morbidity among women.[2] It is estimated that 1.62 billion people worldwide have anemia, with 30.2% of them being women of reproductive age.[18]

The causes of iron deficiency anemia in women are multifactorial and may be attributed to abnormal uterine bleeding, menstruation, and blood loss in the gastrointestinal tract. In low- and middle-income countries, it is also necessary to consider the diagnostic possibilities of malaria, hookworm infection, and schistosomiasis.[2] The risk of iron deficiency anemia increases in women due to pregnancy and menstruation during reproductive cycles. Given its high prevalence and negative consequences, it is considered a public health issue.[3]

Findings reveal a reduced quality of life in non-pregnant women of reproductive age who have iron deficiency anemia, manifesting as pallor, weakness, alopecia, fatigue, lower tolerance to physical exercise, decreased cognitive activity, and irritability.[2,18] If pregnancy occurs during this period, there is a higher likelihood of adverse outcomes, such as maternal or perinatal mortality, low birth weight (3.1 times higher risk), and an increased risk of prematurity (2.6 times higher risk).[18]

Approximately 12% of women begin pregnancy with low or absent iron stores, and during pregnancy, iron requirements increase tenfold to support fetal and placental growth, maternal red blood cell expansion, and potential blood loss during childbirth.[2] Therefore, iron supplementation during pregnancy can be crucial in reducing the prevalence of iron deficiency anemia and its harmful consequences for both the mother and fetus.[19]

Postpartum anemia is associated with depression, fatigue, decreased cognitive activity, and difficulties in breastfeeding. Individuals born to mothers with iron deficiency may experience learning and memory difficulties from childhood into adulthood.[2]

ELDERLY

Anemia is most frequently diagnosed in elder citizens (>65 years of age) rather than younger adults. During the last few years, there have been numerous advances in diagnostics as well as an aging of the general population due to higher life expectancy. The clinical impact of anemia in older patients is relevant as it may be a risk factor for cardiovascular diseases, cognitive limitation, falls and fractures, longer and more recurrent hospitalizations, insomnia and reduction of executive function. [20]

Among the elderly, iron deficiency anemia is the most common type and can result from various etiologies, including nutritional deficiencies and gastrointestinal bleeding.[11,19] Studies have shown that the prevalence of iron deficiency anemia in patients with gastrointestinal bleeding reaches 61%; however, this disorder remains underdiagnosed and undertreated. These bleedings are often chronic and associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), ulcers, colon cancer, or diverticular disease of the colon.[19,21] NSAIDs are frequently used by patients over 65 years old for the management of mild, moderate and severe pain that accompany chronic and degenerative diseases. Their common adverse effects include ulcers and upper and lower gastrointestinal tract bleeding - which the risks increase with age. [22,23]

The most common treatment for iron deficiency anemia is oral ferrous sulfate, which is a simple and low cost treatment. It also presents with disadvantages, such as gastrointestinal adverse effects, long course therapy, limited absorption when associated with diseases that cause chronic inflammation or malignancy in the gastrointestinal tract as well as lack of adherence and ineffectiveness when dealing with ongoing blood loss. Intravenous therapy, such as ferric carboxymaltose may be superior in some scenarios due to quicker and more significant rises in hemoglobin levels and iron reserves in the body in addition to being more tolerable and still being effective with an increased level of hepcidin.[24]

Anemia of inflammation (or anemia of chronic disease) is an important differential diagnosis of iron deficiency anemia, as it results from impaired iron utilization due to the interaction of inflammatory cytokines with hepcidin, which decreases duodenal iron absorption and inhibits its mobilization from storage sites, causing a functional iron deficiency.[11,25]

It is known that approximately 30% of anemia cases in older adults are due to inflammation-related anemia, with common underlying diseases including neoplasms, diabetes, and cardiovascular diseases.[26-28] Its etiology is known to be multifactorial and may occur in a variety of diseases.[29]

Other factors contributing to reduced erythropoiesis efficiency in older adults include cellular senescence, genetic instability, telomere shortening, mitochondrial dysfunction, and altered intercellular communication.[28, 30] Inflammation-related cytokines, such as IL-1, TNF-α, and IL-6, further contribute to erythropoiesis aging and the development of anemia due to specific causes, such as cancer.[27-30] It is believed that these cytokines, as well as hepcidin, inhibit marrow macrophages from releasing iron, although it is not completely comprehended.[29]

In chronic kidney disease, decreased renal mass leads to reduced erythropoietin production, as well as increased hepcidin excretion - also in response to inflammatory cytokines. Hepcidin is a hormone that regulates the iron uptake in the gastrointestinal tract as well as liberating reserved iron. It is regulated by inflammatory cytokines and higher blood concentration may be due to infection, chronic inflammation and kidney failure, as it is renally cleared.[31] This results in decreased duodenal iron absorption and impaired mobilization from storage, reducing iron availability for erythropoiesis and leading to erythropoietin resistance.[25]

Androgenic alterations may also play a role in anemia among older adults. Andropause - or partial androgen deficiency in aging men - can begin as early as age 50, and by age 75, testosterone levels are estimated to be only 65% of those in a young adult.[21] Testosterone is a key factor in erythropoiesis, and its decline leads to reduced red blood cell production.[32,33] It stimulates erythropoietin and decreases hepcidin levels, thus increasing iron utilization.[34]

The prevalence and incidence of myelodysplastic syndromes increase with age, being more common in older adults. These conditions cause progressive bone marrow failure, reducing the ability of the marrow to produce red blood cells and their precursors. Additionally, the aging-related changes in erythropoiesis make the bone marrow more susceptible to the development of myelodysplastic syndromes.[35]

Conclusion

Anemia presents itself as a global public health concern, significantly impacting the quality of life of millions of individuals, particularly in vulnerable groups such as children, reproductive-age women, and the elderly. The complexity of its etiologies - which range from nutritional deficiencies, blood loss and inflammatory processes to hereditary disorders - highlights the need for a multidisciplinary approach to its diagnosis and treatment.

Early recognition and proper management of anemia are essential to prevent complications such as cognitive impairments and compromised development in children, adverse maternal and perinatal outcomes in pregnant women, as well as the deterioration of quality of life and functionality in the elderly. Strategies such as improving diet, food fortification, and supplementation, especially during critical periods like pregnancy, have proven to be effective measures in reducing the prevalence and impacts of this condition.

Thus, the implementation of preventive and therapeutic strategies specific to each group - through targeted public policies, health education and nutritional interventions - is crucial to minimizing socioeconomic impacts and improving clinical outcomes, ultimately contributing to a better quality of life in all age groups.

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