LUMEN ET VIRTUS

Management of iron deficiency anemia in pediatric patients: A systematic review of diagnostic and therapeutic strategies

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ABSTRACT

Objective: The general objective of the present study is to analyze the scientific production on Iron Deficiency Anemia, seeking to identify the main clinical manifestations, as well as the main methods used in the treatment of this pathology. Methodology: It is a systematic review focused on understanding the main aspects of Iron Deficiency Anemia. The research was guided by the question: "What are the main aspects that permeate Iron Deficiency Anemia (IDA) in the pediatric population, as well as what are the diagnostic and therapeutic resources used in clinical practice?". To find answers, searches were performed in the PubMed database using five descriptors combined with the Boolean term "AND". This resulted in 269 articles. 16 articles were selected for analysis. Results: ADF is often caused by factors such as inadequate feeding, early introduction of cow's milk, prematurity, and chronic infections. Treatment includes iron supplementation, either orally or intravenously, but faces adherence-related challenges due to side effects. Prevention, through proper dietary practices and supplementation, along with early diagnosis, is crucial to mitigate the negative

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impacts of ADF and promote healthy development. Conclusion: Public health policies focused on education and the implementation of these strategies are essential to reduce the prevalence and consequences of ADF in vulnerable populations.

Keywords: Anemia, Pediatrics, Diagnosis.

INTRODUCTION

Anemia is the most common hematological anomaly identified in children and continues to be a major global public health problem in both developed and developing countries. In 2019, the World Health Organization (WHO) estimated that the global prevalence of anemia in children aged 6 to 59 months was 39.8%, equivalent to 269 million children, with the highest prevalence rate (60.2%) observed in children from the African continent. Iron deficiency anemia (ADF) affects about 2 billion people worldwide. Children between 2 and 5 years of age and post-menarcheal adolescents are the two pediatric age groups most at risk of developing ADF. In developed countries, the prevalence of ADF in children under 4 years of age is estimated at 20.1%. This prevalence rises to 39% in developing countries. The prevalence of ADF is almost twice as high in children (55%) as in adults (27%) at the time of diagnosis. (Arulparithi et al., 2023) (Resál et al., 2021) (Martinez-Torres et al., 2023)

Anemia is defined as a reduced level of hemoglobin in the blood or mass of red blood cells (RBC) that cannot meet the oxygen needs of peripheral tissues and organs. The laboratory criterion for defining anemia is a hemoglobin level at or below the 2.5th percentile, based on reference data from healthy children. This criterion varies according to age, race, and gender and can also be influenced by environmental factors (Martinez-Torres et al., 2023).

Nutritional anemia usually results from inadequate intake of micronutrients, such as iron, folic acid, riboflavin, vitamins A, B12, and C, which are necessary for blood formation. Other causes of anemia include heavy menstruation, increased iron requirements during pregnancy and in growing children, chronic infections (such as tuberculosis, HIV, hookworm, and malaria), as well as malabsorption, transport, and storage of iron, including hemoglobinopathies. Nutritional iron deficiency (ID) is a disorder caused by low dietary iron intake, increased iron demand, and/or iron loss, as well as low iron bioavailability from staple foods (Turawa et al., 2021).

Iron homeostasis is the balance between the absorption, storage, and recycling of iron by erythroid precursors. Total body iron is distributed in three compartments. Most of the total body iron (at least two-thirds) is within the erythrocytes, in the form of hemoglobin (Hb). A small part (about 15%) is "storage iron", mainly held in ferritin or hemosiderin in the liver and spleen, ready to be mobilized; the remainder (10%) is circulating iron in non-heme and unstored tissues. The latter is bound to serum transferrin, an iron chelator that keeps iron in a soluble, inert, and reduced state, preventing toxic oxidative reactions (Raffaeli et al., 2020).

Dietary iron exists in two forms: as heme iron derived from hemoglobin and myoglobin from meat, and as nonheme iron, which can be extracted from plants and dairy. The bioavailability of heme iron is significantly higher (up to 25%), but even in developed countries, most dietary iron is absorbed in the form of non-heme iron. The bioavailability of the latter is only 5-10% and is impaired by the

consumption of phytates in cereals and vegetables, and by the consumption of polyphenols, tannins and oxalates found in vegetables, some fruits, legumes, coffee and tea. Vitamin C increases the absorption of dietary iron (Mantadakis et al., 2020).

Hepcidin is a peptide hormone produced primarily in hepatocytes. However, neutrophils, macrophages, lymphocytes, pancreatic beta cells, and kidney cells have recently been found to also produce hepcidin. The most discussed function of hepcidin is its ability to regulate iron homeostasis. An increase in hepcidin expression results in a decrease in serum iron concentration, while a reduction in iron synthesis increases the concentration of iron in the bloodstream. The action of hepcidin occurs by binding to ferroportin, preventing the release of iron into the plasma. The function of ferroportin is to transfer iron to plasma after its absorption from the basolateral surface of enterocytes and to store iron in macrophages and hepatocytes that recycle the heme of senescent erythrocytes (Berton and Gambero, 2024). Any infectious disease and/or inflammatory condition upregulates the expression of hepcidin through interleukin 6 (IL-6) and, consequently, decreases iron absorption. Positive-regulated IL-6 is responsible for the characteristic hyposideremic response to acute inflammation. Thus, chronic heart failure, chronic kidney disease, inflammatory bowel diseases, autoimmune rheumatic diseases, and obesity – an often overlooked inflammatory condition that is almost exclusively limited to developed countries – are associated with decreased iron absorption (Mantadakis et al., 2020).

Growing evidence indicates that adverse events early in life (e.g., malnutrition) can have a lasting impact on physical and mental health. A particularly well-studied adverse event early in life is iron deficiency anemia, which affects 40-50% of pregnant women and preschoolers, and is the most common micronutrient deficiency worldwide. ADF during the fetal and early childhood periods has a significant effect on neurodevelopment, resulting in cognitive, socio-emotional, learning, and memory deficits that persist into early adulthood. ADF also carries long-term health risks, including an increased risk of neuropsychiatric disorders such as autism and schizophrenia (Barks et al., 2021) This systematic review article aims to compile and analyze the scientific evidence on the diagnosis and management of Iron Deficiency Anemia in pediatric patients. The objective is to provide a comprehensive and up-to-date view, which synthesizes existing knowledge and identifies gaps in research, guiding future investigations and clinical practices. In-depth analysis of the evidence is intended to be a useful resource for healthcare professionals, researchers, and academics, contributing to the improvement of diagnostic and therapeutic approaches.

METHODOLOGY

This is a systematic review that seeks to understand the main aspects of Iron Deficiency Anemia (IDA) in pediatric patients, as well as to demonstrate the main methods used in the diagnosis

and treatment of the condition, aiming to ensure a greater clinical elucidation of this pathology. For the development of this research, a guiding question was elaborated through the PVO (population, variable and objective) strategy: "What are the main aspects that permeate Iron Deficiency Anemia (IDA) in the pediatric population, as well as what are the diagnostic and therapeutic resources used in clinical practice?"

The searches were carried out through searches in the PubMed Central (PMC) databases. Five descriptors were used in combination with the Boolean term "AND": Anemia, Neonatal Anemia, Anemia Iron-Deficiency, Signs and Symptoms, Pediatrics. The search strategy used in the PMC database was: Anemia AND Anemia, Neonatal; Anemia, Iron-Deficiency AND Anemia, Neonatal ; Anemia, Iron-Deficiency AND Pediatrics e Anemia, Iron-Deficiency AND Signs and Symptoms. From this search, 269 articles were found, which were subsequently submitted to the selection criteria. The inclusion criteria were: articles in English, Portuguese and Spanish; published in the period from 2019 to 2024 and that addressed the themes proposed for this research, in addition, review, observational and experimental studies, made available in full. The exclusion criteria were: duplicate articles, available in the form of abstracts, that did not directly address the proposal studied and that did not meet the other inclusion criteria.

After associating the descriptors used in the searched databases, a total of 269 articles were found. After applying the inclusion and exclusion criteria, 28 articles were selected from the PubMed database, and a total of 16 studies were used to compose the collection.

DISCUSSION

Anemia is one of the main global public health challenges, mainly affecting children aged 0 to 5 years and women of childbearing age. The World Health Organization (WHO) estimates that 42% of children under the age of five suffer from anemia (June et al., 2023). element. Iron deficiency anemia (IDA) impacts about 40% of children under 5 years of age. ADF tends to manifest in late childhood, when iron stores accumulated during pregnancy are depleted, and needs increase due to rapid growth. A second peak occurs in girls during puberty, when accelerated growth coincides with blood loss from menstruation. Poor nutrition or increased consumption of cow's milk contributes to ADF in children. Due to the low iron content in cow's milk, supplementation is often necessary to meet the body's iron needs. Iron deficiency and the resulting anemia can have serious functional consequences, especially for the development of infants and young children. The American Academy of Pediatrics (AAP) has concluded that ADF impairs a child's behavioral development and cognitive performance (Miniello et al., 2021) (Kalff et al., 2022).

The most frequent risk factors for developing iron deficiency in children include prematurity, a nutrient-poor diet, excessive consumption of cow's milk, and chronic blood loss. In infants, the

early introduction of cow's milk is the most relevant dietary factor associated with ADF. Cow's milk is low in iron, and the iron in it is poorly absorbed in the gastrointestinal tract. In addition, cow's milk reduces the absorption of iron from other food sources due to its high casein and calcium content. Casein binds to iron and prevents its release in the free form necessary for absorption by the duodenal mucosa. High calcium consumption is also known to inhibit the iron transporter of human divalent metal transporter 1 (hDMT1) at the luminal level. Strictly avoiding cow's milk in the first 12 months of life is crucial in preventing ADF (Martinez-Torres et al., 2023).

The WHO defines anemia in a population as a mild, moderate, or severe public health problem if its prevalence is 5-20%, 20-40%, or >40%, respectively. Most WHO countries face a moderate to severe public health problem with anemia, i.e., more than 20% of women and young children are affected. In developing countries, diets with low iron bioavailability are the main cause of iron deficiency anemia, since the diet is predominantly composed of cereal- or legume-based foods, often rich in phytates, and many common foods or beverages contain phenols that bind to iron, while meat consumption, poultry and fish, which are rich in iron and zinc, is often low for economic, cultural, and/or religious reasons. Maintaining an adequate iron balance in resource-limited settings is difficult due to poverty, since iron-rich foods with high bioavailability are animal-based and expensive and/or scarce (Mantadakis et al., 2020).

In developed countries, dietary errors and gastrointestinal and genital blood loss are the most common causes of ADF. In industrialized countries, inadequate eating habits, such as prolonged breastfeeding without iron supplementation after the fourth month of life, decreased consumption of iron-fortified milk, introduction of fresh cow's milk before the first birthday, consumption of cow's milk > 500 mL/day, prolonged use of bottle feeding beyond the twelfth month of life, bottle-feeding use in bed, preference for poultry over red meat, and vegan diets are associated with ADF. In addition, celiac disease, symptomatic giardiasis, gastrectomy, reduced gastric acidity, and low iron intake for cultural or religious reasons are causes of iron deficiency and ADF due to reduced iron supply (Mantadakis et al., 2020).

Several epidemiological studies and meta-analyses indicate that persistent Helicobacter pylori infection in the gastric mucosa can lead to iron deficiency or iron-deficiency anemia (ADF), especially in certain populations of children and adolescents. In addition, it has been shown that H. pylori infection may be closely associated with recurrent and/or refractory iron deficiency and ADF. However, the pathogenesis and specific risk factors leading to this clinical outcome in H. pylori-infected children are not yet well understood. In general, most pediatric patients with H. pylori-associated FAA have no evidence of overt blood loss due to gastrointestinal hemorrhagic lesions (Kato et al., 2022).

The most robust evidence on the relationship between iron deficiency anemia (IDA) and thrombosis in children comes from two case-control studies that investigated the connection between FAA and stroke in 36 children and 143 healthy controls. In both studies, ADF was defined as serum ferritin levels below 12 µg/L, along with hemoglobin and mean corpuscular volume below the reference limits for age and sex. Children with symptoms of arterial ischemic stroke or cerebral sinus venous thrombosis, confirmed by computed tomography or magnetic resonance imaging, were included as cases in both studies. Thrombocytosis has been identified as a platelet count greater than 450 × 10^9/L. ADF was found to be a significant risk factor for stroke development in both studies (Kalff et al., 2022).

Early Childhood Caries (IPC) is defined by the presence of one or more decayed surfaces (cavitated or not), absent or restored (caries) surfaces on any baby tooth in children under 6 years of age. Both IPC and FAD are multifactorial diseases influenced by social determinants of health. One of the relational factors is evidenced by malnutrition, which has a negative impact on the quality of saliva during early childhood. The reduction in salivary flow compromises the buffering capacity of saliva, impairing its preventive function against cavities. In addition, iron has a karyostatic effect, due to acid-resistant protective coatings, formed by hydrated iron, which cover the surface of the enamel and prevent its dissolution. To initiate the formation of apatite, these ions adsorb calcium and phosphate ions from saliva, replacing minerals lost during the caries process. Iron can also have a significant inhibitory effect on the growth of Streptococcus mutans, the early presence of which is directly associated with the severity of dental caries (Easwaran et al., 2022).

Iron deficiency can negatively impact the developing brain in several ways. It can compromise the growth of neurons in the hippocampus and disrupt the process of myelination, which isolates nerve fibers for effective signaling. This deficiency can also affect the metabolism of neurotransmitters such as monoamines and aldehyde oxidase, resulting in reduced levels of neurotransmitters and a possible decrease in seizure threshold. In addition, low serum ferritin levels, in conjunction with fever, can aggravate adverse effects on the brain, which can result in seizures. Seizures caused by temperatures higher than 100.4°F (38°C) are called febrile seizures (CF). Iron deficiency can be considered a potential risk factor for CF (Bakkannavar et al., 2024).

About half of the iron needed for infant growth and development must be absorbed by the mother before birth, during the third trimester of pregnancy. Therefore, most healthy full-term babies have adequate iron reserves at birth to meet their needs until six months of age. These iron stores are gradually depleted and breast milk alone is no longer enough to meet the baby's iron needs. The WHO and the Pan American Health Organization (PAHO) recommend exclusive breastfeeding during the first six months of life, combined with adequate complementary feeding after this period. The complementary food introduction (CA) phase, which usually occurs between 6 and 23 months,

is characterized by rapid growth and development, exposing infants to a higher risk of nutritional deficiencies or excesses, especially ADF, which is more common at this stage. Therefore, correct feeding practices and complementary foods (semi-solids, solids, and liquids other than breast milk, infant, transitional, and toddler formulas) can prevent malnutrition (Miniello et al., 2021).

To prevent ADF, the American Academy of Pediatrics recommends that babies born before 37 weeks of gestation and who are breastfed receive elemental iron at a dose of 2 mg/kg/day, either through medical iron, iron-fortified milk, or complementary foods, starting in the first month and extending to twelve months of life (Mantadakis et al., 2020).

There is no single gold standard test for the detection of iron deficiency anemia. Serum hemoglobin or hematocrit are usually the first tests used to identify anemia. However, these tests do not allow differentiating between ADF and other causes of anemia. Additional tests such as serum ferritin, transferrin saturation, erythrocyte protoporphyrin, and C-reactive protein (CRP) are required to detect iron deficiency. Haemoglobin or haematocrit has an estimated sensitivity of 73% for the detection of ADF, but a reduced specificity of 25%, as approximately half of anemia cases are due to causes other than iron deficiency (Jullien, 2021).

Anemia is generally defined as hemoglobin <11g/dL in infants and young children aged 6 months to 5 years, hemoglobin <11.5g/dL for children 5 to 12 years, and hemoglobin <12 g/dL for female adolescents over 12 years of age (<13g/dL for male adolescents). FAA is a microcytic and hypochromic anemia, i.e., it is characterized by low mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). In addition, there is a low red blood cell count, high red blood cell width of distribution (anisocytosis), and low reticulocyte count or reticulocyte production index, low hemoglobin A2, and frequent thrombocytosis. ADF, along with infections, is the most common cause of high platelet count in the world (Mantadakis et al., 2020).

An iron profile, including serum iron, transferrin, total iron-binding capacity (TIBC), and ferritin, should also be ordered. Transferrin is a protein that binds to and transports serum iron. Together with transferrin, TIBC reflects the carrying capacity of iron. Ferritin is the protein responsible for intracellular iron storage, and its level reflects an individual's iron stores. Although a ferritin level of 12 to 15 ng/mL has traditionally been considered the cut-off point for diagnosing iron deficiency, a ferritin level <30 ng/mL is associated with a higher sensitivity and specificity (92% and 98%, respectively) for identifying people with iron deficiency (Martinez-Torres et al., 2023).

Biochemically, ADF is characterized by low serum iron levels, reduced serum ferritin, decreased transferrin saturation, increased total iron-binding capacity, elevated levels of soluble serum transferrin receptors (sTfR), elevated serum zinc protoporphyrin (ZnPP) levels, and low levels of serum hepcidin-25, the active form of hepcidin. Ferritin can be misleading in children with ADF

and concomitant infections as it is an acute-phase protein. Unfortunately, measurements of sTfR and ZnPP are not widely available and expensive, while hepcidin is used almost exclusively for research purposes, given the absence of a gold-standard measurement assay and awaiting international standardization (Mantadakis et al., 2020).

Iron deficiency may go unnoticed until the patient reaches critically low hemoglobin levels. This delay in diagnosis can put patients at risk for rare but serious complications such as thrombosis, stroke, congestive heart failure, and even death. Iron deficiency has also been linked to lasting impacts on neurological development. Standardized test results in children aged 11 to 14 years who suffered from iron deficiency in childhood show lower performance on six different tests, including total IQ and wide-range arithmetic and reading tests (Martinez-Torres et al., 2023).

Primary treatment for ADF usually involves correcting iron deficiency through iron-rich foods and/or oral iron supplementation. There are several oral formulations of iron available, with ferrous sulfate being the most widely used globally. Other formulations include iron polymaltose complex (IPC), iron bisglycinate chelate, ferrous ascorbate, colloidal iron, iron-zinc, and lactoferrin. Iron administered orally (in liquid formulas or tablets) is usually effective, but side effects, difficulties swallowing tablets, and the unpleasant taste can reduce adherence to treatment, especially in children. After starting supplementation, it takes about 24 hours for intracellular enzymes to be replenished, followed by an increase in hemoglobin over the course of a month, and iron storage takes one to three months. A significant proportion of patients experience gastrointestinal side effects (70%), such as nausea and gastroesophageal reflux, which may result in non-adherence to treatment. Gastrointestinal toxicity is the most common cause of non-compliance and treatment failure. (Arulparithi et al., 2023) (Aksan et al., 2022) (Martinez-Torres et al., 2023)

Intravenous (IV) iron therapy offers an alternative that can be considered a second-line treatment when oral iron therapy is unsuccessful. Intravenous iron therapy can also be used as first-line treatment for specific groups of patients, including children with gastrointestinal disorders, chronic kidney disease (CKD), or restless leg syndrome, and children on prolonged parenteral nutrition. Intravenous iron preparations have been available for some time, and iron sucrose is a widely used type for the treatment of ID/IDA. However, iron sucrose requires repeated dosing every other day. Newer IV iron preparations, such as ferric carboxymaltose (FCM), ferumoxytol, and iron isomaltoside 1000, are optimized for dosing and allow correction of iron deficiency with a single infusion. FCM can be administered as a single dose within 15 minutes and was recently approved by the US Food and Drug Administration (FDA) for the treatment of IDA in pediatric patients over the age of 1 year who have an intolerance or a poor response to oral iron (Aksan et al., 2022).

The largest study of ferric carboxymaltose in the pediatric age group was a single-center retrospective study that included 225 patients aged 2 months to 20.3 years with FAA of various

etiologies. Although the primary objective of this study was to evaluate phosphate levels in children treated with FCM, iron parameters were also recorded, showing significant improvements in hemoglobin, mean corpuscular volume, and ferritin values. Regarding the adverse effects of FCM therapy, studies in children under 14 years of age with ADF due to various causes showed, in a retrospective study with 176 children, the occurrence of hypotension (in one patient), rash (in four patients), and fever (in two patients). In another retrospective study with 60 children, three episodes associated with mild adverse effects (type of event not reported) and one episode of extravasation were identified in a total of 65 episodes of FCM administration (Aksan et al., 2022).

CONCLUSION

Iron deficiency anemia (IDA) poses a significant public health challenge, especially among young children and women of childbearing age. The impact of this condition is profound, affecting not only the physical but also the cognitive and behavioral development of children. Factors such as inadequate feeding, prematurity, early introduction of cow's milk, and chronic infections contribute to the emergence and persistence of IDA. In response to this reality, preventive and therapeutic interventions are essential. Strategies such as iron supplementation, both oral and intravenous, are key, but face challenges related to adherence and side effects. In addition, early diagnosis is crucial to avoid serious complications, such as stroke and neurological impairment. Therefore, public health policies focused on the proper prevention and treatment of ADF, especially in vulnerable populations, are imperative to mitigate the effects of this condition and promote healthy development.

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