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REVIEW ARTICLE

Anemia in children: a pediatrician's view

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Abstract

Anemia is defined as a hemoglobin level that is two standard deviations below the mean for age. After children reach the age of 12, the hemoglobin norm can be further divided into gender-specific ranges. When a patient presents with anemia, it is important to establish whether the abnormality is isolated to a single cell line [red blood cells (RBC) only] or whether it is part of a multiple cell line abnormality. In children, anemia is usually caused by decreased RBC production or increased RBC turnover. Anemia is usually classified based on the size of RBC (microcytosis, normocytosis, or macrocytosis) as measured by the mean corpuscular volume. Although iron deficiency anemia is usually microcytic, some patients may have normocytic blood cells. From a practical point of view, it is better to use in children the etiologic classification of anemia which includes impaired red cell formation, blood loss and hemolytic anemia. Most children with anemia are asymptomatic, and the condition is detected on screening laboratory evaluation. Iron deficiency can be treated with oral iron, intravenous iron, and/or blood transfusion, depending on the patient`s hemoglobin levels, tolerance and co-morbidity. Oral iron salts are usually the first line of treatment for uncomplicated iron deficiency, but are poorly absorbed and lead to gastrointestinal side effects. In some cases, iron refractory iron deficiency anemia (IRIDA), a hereditary recessive anemia refractory to oral iron, occurs. IRIDA shows a slow response to intravenous iron and partial correction of anemia.

Key words: anemia, iron deficiency, iron refractory iron deficiency anemia (IRIDA)

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Anemia is a public health problem that affects both rich and poor countries [1]. Worldwide, anemia affects up to 50% of children under 5, especially children from low-income families [2]. Anemia with iron deficiency is the most common form of anemia.

Infants and children needs iron for the proper neurological development, differentiation of brain cell, myelinization of neurons, and as a cofactor for enzymes that synthesize neurotransmitters.

This is why iron deficiency/anemia negatively impacts on the fundamental aspects of growth and intellectual developments with potential long-term consequences [2, 3]. We diagnose anemia when a hemoglobin level is two standard deviations below the mean for age. We should remember that the hemoglobin level in children above 12 of age is gender-specific [4]. In some patients anemia is limited only to the red blood cell line [RDC] and in others it coexists with damage to other cell lines in bone marrow [4] When anemia coexists with damage to other cell lines we should primary diagnose bone marrow diseases (aplastic anemia, leukemia) or an immunological disorders [5]. Iron deficiency is one of the main causes of anemia in patients with chronic kidney disease. We also diagnose anemia in patients with, celiac disease, non-celiac gluten sensitivity, an autoimmune atrophic gastritis and in patients with bowel disease in which it is more frequent than in Crohn's disease. Decreased production or destruction of RDC are the main cause of anemia in children [6].

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One of the classification of anemia is based on the size of RBC, which specifies the mean corpuscular volume (MCV). With MCV we distinguish microcytic anemia (MCV <80 fL), normocytic anemia (80–100 fL), or macrocytic anemia (>100 fL).

RBC distribution width is a measure of the size variance of RBCs. A low RBC distribution width suggests uniform cell size, whereas an elevated width (>14%) indicates RBCs of multiple size.

From a practical point of view, it is better to use in children the etiologic classification of anemia which includes impaired red cell formation (deficiency, bone marrow failure, infiltration) blood loss and hemolytic anemia (corpuscular, extracorpuscular). Due to the consequences of anemia, the American Academy of Pediatrics (AAP) and the World Health Organization (WHO) recommend testing for anemia in children at one year of age [2]. In Polish children, we recommend testing for anemia at 3, 6 and 12 months, and also in children with feeding problem, poor growth, inadequate dietary iron intake, and during adolescence, especially in girls [7].

In most children anemia is asymptomatic, and we diagnose it based on a medical history, physical examination or additional tests. Symptoms indicative of anemia are irritability or pica, jaundice, shortness of breath, or palpitations.

In medical history important are questions about prematurity, low birth weight, diet, chronic disease, and a family history of anemia. In the physical examination, we pay attention to jaundice, tachypnoe, tachycardia, and heart failure, especially in children with severe or acute anemia. The basic research of anemia is a complete blood count, reticulocyte count, serum ferritin level reflecting iron stores and transferrin.

Though serum ferritin is a good indicator of stored iron, as an acute phase protein may be increased with inflammation or chronic diseases. Therefore, it should not be tested in these states for assessing iron stocks.

A blood iron test assesses its current concentration in blood, but does not specify the amount of iron available in the body, hence this result is interpreted along with others iron tests.

Total iron-binding capacity (TIBC) measures all the proteins in the blood that are available to bind with iron, including transferrin. unsaturated iron-binding capacity (UIBC) measures the portion of transferrin that has not yet been saturated. UIBC also reflects transferrin levels.

Transferrin saturation is a calculation that reflects the percentage of transferrin that is saturated with iron.

Soluble transferrin receptors (sTfRs) are proteins found in the blood which can be elevated with iron deficiency. The sTfR test is not available at all centers, but because it is not an acute phase reactant, it is useful for assessing iron stores in patients with chronic diseases.

If the anemia is microcytic, we should look for iron deficiency, thalassemia and anemia of chronic disease. Iron deficiency, chronic disease, hemolysis, immune-mediated destruction, and bone marrow disorders are the most common causes of normocytic anemia. Macrocytic anemia is uncommon in children. It is caused by deficiency of vitamin B_{12}, and folic acid, hypothyroidism and hepatic disease.

The main causes of anemia in newborns are hemorrhage, hemolysis or failure of red cell production. Anemia in infants and toddlers is caused by: failure of red cell production, hemorrage, hemolysis. Anemia in older children and adolescents is caused by failure of red cell production, hemorrage, hemolysis.

As previously stated, iron deficiency anemia is the most common type in children. Although iron deficiency anemia is usually microcytic, some patients may have normocytic blood cells [2, 8]. Anemia is most common in children during late infancy/early childhood because of rapid growth, exhaustion of gestational iron and low levels of dietary iron. The second period of increased occurrence of anemia is adolescence, due to rapid growth, suboptimal iron intake and menstrual blood loss in females [5].

Children at the aged 1–3 years should receive 7 mg elementary iron daily in food. We must remember that consumption of large quantities of non–iron-fortified cow's milk favors the occurrence of iron deficiency anemia.

For older children in areas of high anemia prevalence, the WHO recommends intermittent iron supplementation (potentially once or twice a week) for pre-school and school-age children and adolescents [9].

When we delayed umbilical cord clamping for 60––120–180 sec after delivery, iron status in infants aged 2–6 month may be improved, however, it does not last longer than 12 months [2, 9–11].

Exclusively breastfed preterm infants, except for those who have had multiple blood transfusions. should receive prophylactically 2 mg elementary iron per kg per day from age 1–12 month [2, 12].

Full-term infants do not require prophylaxis with iron, for their pregnant iron supplies are sufficient for the first 4–6 months of life [2, 13].

As recommended the AAP full-term exclusively breastfed infants should receive 1 mg per kg per day of elementary iron supplementation at age 4 months until introduced into the diet foods that contain the right amount of iron [2, 12, 13]. Formula-fed infants often receive adequate amounts of iron, and thus rarely require further supplementation [12]. Full-term infants (4–6 month to 1 year) require 11 mg iron per day and children aged 1–3 years require 7 mg iron per day [2, 14, 15].

Patient's hemoglobin levels, tolerance of anemia and co-morbidity decide on the form of iron administration, oral

iron, intravenous iron, and/or blood transfusion. Oral forms of iron as ferrous or ferric salts are are most often used for the sake of their availability, ease of administration, and relatively low cost. We currently have:

1) iron (II) compounds (ferrous sulphate, ferrous glycine sulphate, ferrous fumarate, ferrous gluconate);
2) iron (III) complexes [iron (III) hydroxide polymaltose complex, iron (III) succinyl protein complex];
3) elemental iron (carbonyl iron);
4) sucrosomal iron.

During the therapy with oral iron salts, in some patients they are observed the gastrointestinal side effects, caused by poor drug absorption [16]. Some new iron preparations increase their tolerability.

One of these is sucrosomal iron, absorbed as a vesicle-like structure, bypassing the conventional iron absorption pathway. Therefore sucrosomal iron is well tolerated and more bioavailable than other iron salts salts [17, 18].

The properties of sucrosomal iron make it recommended for patients at which iron salts are inefficacious and also in iron deficiency prophylaxis. This drug can be used for initial or maintenance treatment [17].

Intravenous iron is administered to the patients with intolerance to oral iron salt, or when the treatment is inefficacious [19]. Intravenous iron preparations include ferric gluconate, iron sucrose, low molecular weight iron dextran, ferric carboxymaltose, ferumoxytol and iron isomaltose. Due to the occasional anaphylactic reactions after the intravenous iron administration, treatment must lead only by staff trained to manage anaphylactic reactions, and where resuscitation facilities are immediately available [20].

An indication to the red cell transfusion are very severe iron deficiency anemia and hemodynamic instability. After the red cell transfusion we observe transient rise of haemoglobin, as a result, it increases oxygen-carrying capacity. In patients who achieved hemodynamic stability the iron supplementation should be considered [17, 21].

The first description of the patients with iron unresponsive anemia, malabsorption of medical iron and a partial but incomplete hematological response to parenteral dextran occured in 1981 [22, 23].

After 16 years, in 1997, there was a report about the 18-month old African child with iron resistant iron deficiency anemia and severe microcytosis [24]. His anemia was unresponsive to oral iron supplementation and persisted after iron stores were replete. Most of the reported cases have been children, who despite anemia, had normal growth, development and intellectual performance [22, 24, 25].

Iron refractory iron deficiency anemia (IRIDA), presented above, is a hereditary recessive anemia due to a defect in the *TMPRSS6* gene encoding matriptase 2. This protein plays a role in down-regulating hepcidin, the key regulator of iron homeostasis [22, 26].

The IRIDA patients are characterized by hypochromic, microcytic anemia, very low serum iron, and transferrin saturation levels. However, serum ferritin levels are mostly within the normal range or even slightly elevated following intravenous iron treatment. The degree of anemia varies, being mostly mild and more pronounced in childhood. Anemia is not detectable at birth. The phenotype develops only after the neonatal period [22]. In most patients, oral iron is ineffective in correcting anemia, and patients must receive intravenous iron. The response to parenteral administration of iron is variable but generally leads to a progressive increase in hemoglobin levels. Correction of anemia is much slower than in patients with acquired iron deficiency. Hemoglobin levels rarely normalize, microcytosis persists and transferrin saturation remains below normal value. Serum ferritin increases following iron injections, somehow in a dose-dependent manner [22].

Anemia classification and diagnosis in children is a very complex challenge, although it must be remembered that the main cause of anemia is iron deficiency. Oral iron is the first-line treatment for iron deficiency in pediatric populations [12].

Authors' contributions

MM — sole author.

Conflict of interest

None.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

References

1. WHO. Worldwide prevalence of anemia 1993–2005. http://whqlibdoc.who.int/publications/2008/9789241596657_eng.pdf (May 2, 2021).
2. Wang M. Iron deficiency and other types of anemia in infants and children . Am Fam Physician. 2016; 93(4): 270–278, indexed in Pubmed: 26926814.
3. Farias ILG, Colpo E, Botton SR, et al. Carbonyl iron reduces anemia and improves effectiveness of treatment in under six-year-old children. Rev Bras Hematol Hemoter. 2009; 31(3): 125–131.
4. Short MW, Domagalski JE. Iron deficiency anemia: evaluation and management. Am Fam Physician. 2013; 87(2): 98–104, indexed in Pubmed: 23317073.

5. Lanzkowsky P. Classification and diagnosis of anemia during childhood. In: Manual of pediatric haematology and oncology. Elsevier Academic Press, Cambridge 2005: 1–11.
6. Janus J, Moerschel SK. Evaluation of anemia in children . Am Fam Physician. 2010; 81(12): 1462–1471, indexed in Pubmed: 20540485.
7. Lachowicz JI, Nurchi VM, Fanni D, et al. Nutritional iron deficiency: the role of oral iron supplementation. Curr Med Chem. 2014; 21(33): 3775–3784, doi: 10.2174/0929867321666140706143925, indexed in Pubmed: 25005180.
8. Bermejo F, García-López S. A guide to diagnosis of iron deficiency and iron deficiency anemia in digestive diseases. World J Gastroenterol. 2009; 15(37): 4638–4643, doi: 10.3748/wjg.15.4638, indexed in Pubmed: 19787826.
9. Hutton EK, Hassan ES. Late vs early clamping of the umbilical cord in full-term neonates: systematic review and meta-analysis of controlled trials. JAMA. 2007; 297(11): 1241–1252, doi: 10.1001/jama.297.11.1241, indexed in Pubmed: 17374818.
10. Andersson O, Hellström-Westas L, Andersson D, et al. Effect of delayed versus early umbilical cord clamping on neonatal outcomes and iron status at 4 months: a randomised controlled trial. BMJ. 2011; 343: d7157, doi: 10.1136/bmj.d7157, indexed in Pubmed: 22089242.
11. Andersson O, Lindquist B, Lindgren M, et al. Effect of delayed vs early umbilical cord clamping on iron status and neurodevelopment at age 12 months: a randomized clinical trial. JAMA Pediatr. 2014; 168(6): 547–554, doi: 10.1001/jamapediatrics.2013.4639, indexed in Pubmed: 24756128.
12. Baker RD, Greer FR. Committee on Nutrition American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age). Pediatrics. 2010; 126(5): 1040–1050, doi: 10.1542/peds.2010-2576, indexed in Pubmed: 20923825.
13. Flerlage J, Engorn B. eds. The Harriet Lane handbook: a manual for pediatric house officers. 20th ed. Saunder/Elsevier, Philadelphia 2015: 305.
14. Biondich PG, Downs SM, Carroll AE, et al. Shortcomings in infant iron deficiency screening methods. Pediatrics. 2006; 117(2): 290–294, doi: 10.1542/peds.2004-2103, indexed in Pubmed: 16452345.
15. Camaschella C. Iron-deficiency anemia. N Engl J Med. 2015; 372(19): 1832–1843, doi: 10.1056/NEJMra1401038, indexed in Pubmed: 25946282.
16. Tolkien Z, Stecher L, Mander AP, et al. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. PLoS One. 2015; 10(2): e0117383, doi: 10.1371/journal.pone.0117383, indexed in Pubmed: 25700159.
17. Gomez-Ramirez S, Brilli E, Tarantino G, et al. Sucrosomial ® iron: a new generation iron for improving oral supplementation . Pharmaceuticals (Basel). 2018; 11(4): 97, doi: 10.3390/ph11040097, indexed in Pubmed: 30287781.
18. Fabiano A, Brilli E, Fogli S, et al. Sucrosomial® iron absorption studied by in vitro and ex-vivo models. Eur J Pharm Sci . 2018; 111: 425–431, doi: 10.1016/j.ejps.2017.10.021, indexed in Pubmed: 29055735.
19. Auerbach M, Adamson JW. How we diagnose and treat iron deficiency anemia. Am J Hematol. 2016; 91(1): 31–38, doi: 10.1002/ajh.24201, indexed in Pubmed: 26408108.
20. Cook JD. Diagnosis and management of iron-deficiency anaemia. Best Pract Res Clin Haematol. 2005; 18: 319–332, doi: 10.1016/j.beha.2004.08.022, indexed in Pubmed: 15737893.
21. Muñoz M, Gómez-Ramírez S, Besser M, et al. Current misconceptions in diagnosis and management of iron deficiency. Blood Transfus. 2017; 15(5): 422–437, doi: 10.2450/2017.0113-17, indexed in Pubmed: 28880842.
22. DeFalco L, Sanchez M, Silvestri L, et al. Iron refractory iron deficiency anemia. Haematologica. 2013; 98(6): 845–853, doi: doi.org/10.3324/haematol.2012.075515.
23. Buchanan GR, Sheehan RG. Malabsorption and defective utilization of iron in the siblings. J Pediatr. 1981; 98(5): 723–728, doi: 10.1016/s0022-3476(81)80831-1, indexed in Pubmed: 7229750.
24. Andrews NC. Iron deficiency: lessons from anemic mice. Yale J Biol Med. 1997; 70(3): 219–226, indexed in Pubmed: 9544492.
25. Pearson HA, Lukens JN. Ferrokinetics in the syndrome of familial hypoferremic microcytic anemia with iron malabsorption . J Pediatr Hematol Oncol. 1999; 21(5): 412–417, doi: 10.1097/00043426-199909000-00014, indexed in Pubmed: 10524456.
26. Mells MA, Cau M, Conglu R, et al. A mutation in the TMPRSS6 gene encoding a transmembrane serin pro-tease that suppresses hepcidin production, in familial iron deficiency anemia refractory to oral iron. Haematologica. 2008; 93(10): 1473–1479, doi: 10.3324/haematol.13342, indexed in Pubmed: 18603562.