

TOPIC HIGHLIGHT

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A guide to diagnosis of iron deficiency and iron deficiency anemia in digestive diseases

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Abstract

Iron deficiency (ID), with or without anemia, is often caused by digestive diseases and should always be investigated, except in very specific situations, as its causes could be serious diseases, such as cancer. Diagnosis of ID is not always easy. Low serum levels of ferritin or transferrin saturation, imply a situation of absolute or functional ID. It is sometimes difficult to differentiate ID anemia from anemia of chronic diseases, which can coexist. In this case, other parameters, such as soluble transferrin receptor activity can be very useful. After an initial evaluation by clinical history, urine analysis, and serological tests for celiac disease, gastroscopy and colonoscopy are the key diagnostic tools for investigating the origin of ID, and will detect the most important and prevalent diseases. If both tests are normal and anemia is not severe, treatment with oral iron can be indicated, along with stopping any treatment with non-steroidal anti-inflammatory drugs. In the absence of response to oral iron, or if the anemia is severe or clinical suspicion of important disease persists, we must insist on diagnostic evaluation. Repeat endoscopic studies should be considered in many cases and if both still show normal results, investigating the small bowel must be considered. The main techniques in this case are capsule endoscopy, followed by enteroscopy.

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Key words: Anemia; Iron-deficiency; Iron deficiency anemia

INTRODUCTION

Iron deficiency (ID) is defined as the decrease of the total content of iron in the body. Iron deficiency anemia (IDA) occurs when ID is sufficiently severe to reduce erythropoiesis. This type of anemia is the most frequent chronic anemia. ID may be the result of either excessive loss or, less frequently, decreased absorption. In general, the iron absorbed daily equals the amount needed to compensate its loss, so that the overall iron pool remains stable. This fine balance is easily broken, because the capability to absorb iron orally is limited. When the inputs are less than necessary or, more frequently, when the outputs increase and cannot be compensated for, ID and finally IDA, develops. In many cases, these alterations will be secondary to gastrointestinal disease. IDA occurs in 2%-5% of adult males and postmenopausal women in the developed world^[1,2]. ID, with or without anemia, is even more frequent. It is a common cause of consulting a gastroenterologist (4%-13% of all referred patients)^[3]; however, there is only one clinical guide published that deals with this clinical entity and the evidence level for most conclusions is medium-low, due to the paucity of reliable clinical data^[1]. In addition, for similar reasons, many of the patients treated by gastroenterologists will develop ID and IDA. This data underscores the importance of anemia in our clinical practice. Using a therapeutic iron course has been suggested as diagnostic test of ID. This is a reasonable approach only for people at high risk of physiological ID, such as adolescents and pregnant women^[4]. However, in daily clinical practice it is not unusual to find patients who have received several cycles of iron treatment before assessing the potential cause of anemia. This strategy leads to belated evaluation, especially in young females and in patients with a

prior history of anemia, resulting in significant delay in etiological diagnosis of anemia^[5]. In this sense, except in very specific situations, ID with or without anemia should always be investigated because it can be caused by potentially serious diseases^[1]. We will review the etiology and laboratory diagnosis of chronic ID and IDA to establish recommendations on the practical management of this clinical entity.

ETIOLOGY OF ID OR IDA

There are many potential causes of ID and IDA and some of them are very relevant. These causes are clearly different in developing and in developed countries. Deficient intake is the most frequent etiology in the former, whereas other important diseases are potentially implicated in the case of the latter.

In developed countries, the likeliest cause of anemia in each patient depends on age and sex. In women of childbearing age, excessive menstrual loss is the most frequent etiology, while in postmenopausal women and in males, digestive diseases are the main causes^[3,6]. Taking both these data and a detailed clinical history into account, we will plan diagnostic strategy in each case. However, these assumptions should not lead to errors in dealing with IDA or ID, such as not to investigate anemia in women assuming non-diagnosed gynaecological problems, because that attitude leads to a significant delay in detecting important diseases^[5].

In addition to digestive disorders, gynaecological diseases, urological diseases and other specific situations, such as intravascular hemolysis, the etiology of IDA (Table 1) includes aspects that exceed the purposes of this article. Focusing on digestive diseases, the etiology of ID and IDA of gastrointestinal origin can be divided into two groups: situations with increased loss of iron (the most common in developed countries), and those with decreased iron absorption. In the former, the blood loss can occur in the form of visible bleeding (melena, hematemesis, rectal bleeding) or hidden bleeding, which might be more difficult to diagnose. Among the diseases causing the blood loss we should emphasize, by frequency and importance, benign or malignant gastrointestinal tumors of the colon, stomach, esophagus and small intestine, peptic ulcer and reflux disease, use of non-steroidal anti-inflammatory drugs (NSAIDs), and inflammatory bowel disease. The possible existence of a malignancy as the source of anemia, which leads to early completion of endoscopic examinations in this clinical scenario, is of great concern. In the National Health and Nutrition Examination Survey and Epidemiologic Follow-up Study carried out in the USA on a cohort of 9024 individuals (aged between 25 to 74 years old without prior diagnosis of gastrointestinal malignancy), hemoglobin levels and iron saturation were determined. No case of ID in premenopausal women was determined to be due to malignancies. Among men and postmenopausal women with IDA [Relative Risk (RR) = 31, 95% confidence interval (CI): 9-107] or ID without anemia (RR = 5,

Table 1 Causes of iron deficiency anemia

Digestive disorders
Increased losses of iron
Cancer/polyp: colon, stomach, esophagus, small bowel
Peptic ulcer, esophagitis
NSAID use
Inflammatory bowel disease: ulcerative colitis, Crohn's disease
Intestinal parasites
Vascular lesions: angiodysplasia, watermelon stomach
Meckel's diverticulum
Reduced iron absorption
Celiac disease
Bacterial overgrowth
Whipple's disease
Lymphangiectasia
Gastrectomy (partial and total) and gastric atrophy
Gut resection or bypass
Urological and gynecological disorders
Intravascular hemolysis
Prosthetic valves and cardiac myxomas, paroxysmal nocturnal hemoglobinuria, marathon runners, multiple blood donations
Deficient iron intake

95% CI: 1-21) an increased risk of being diagnosed with cancer within the subsequent two years was observed^[7]. Therefore, gastrointestinal malignancies are uncommon in premenopausal women with ID or IDA, but in men and postmenopausal women with ID or IDA gastrointestinal malignancies are more common than in individuals with normal hemoglobin and iron levels.

Reduced iron absorption is the second category of ID causes of digestive origin, and can be caused by celiac disease, atrophic gastritis, and postsurgical status (gastrectomy, intestinal resection) among others. Celiac disease is very relevant and specific evaluation to exclude it must be performed. In a study on patients referred to a specialized gastroenterological consultation because of ID or IDA, celiac disease was finally the diagnosis in 10% of cases^[8]; other authors described that at least 2%-3% of patients with IDA are finally diagnosed as celiac disease^[3,6]. The prevalence of this disease worldwide is approximately 1%, and it is probably under diagnosed^[9]. Microscopic alterations in the duodenal mucosa in non-treated celiac disease patients will lead to them becoming refractory to oral iron treatment. This has also been described in patients with autoimmune atrophic gastritis and gastritis due to *Helicobacter pylori* (*H pylori*)^[10-12]. Gastroscopy with biopsies, allowing us to detect the presence of atrophy with or without *H pylori*, is essential. The positivity of autoantibodies (anti-intrinsic factor or anti-parietal cell) supports the diagnosis of autoimmune atrophic gastritis^[13]. Regarding the possible role of *H pylori* in IDA, a recent meta-analysis indicated that the infection is associated with depleted iron deposits. The mechanism by which *H pylori* induces this alteration is not clear, but it appears to involve gastrointestinal blood loss, diminished iron absorption from the diet, and increased consumption of iron by the bacteria. The authors suggest that the impact of eradication of *H pylori* in the improvement of the iron deposits must be evaluated in large controlled trials^[14]. Finally, it must be pointed out that in our environment,

a deficit of dietary iron not associated with any other pathology will rarely be the cause of ID or IDA.

CLINICAL MANIFESTATIONS

The clinical picture varies greatly from one case to another, and it is produced both by the anemia itself and by the lack of iron, which is essential for cellular energy metabolism. Symptoms depend greatly on the speed of onset of anemia, its severity, and the characteristics of the patient. Thus, IDA or ID can be detected in an asymptomatic individual on a screening-analysis, or in a person with symptoms that include general weakness, fatigue, irritability, poor concentration, headache, and intolerance to exercise. These symptoms appear even in the figures for ID with normal hemoglobin levels. Patients often show relatively few symptoms spontaneously. Although the impact of ID on the quality of life of the subject is high, they often get used to their symptoms and these are assumed as normal. The patient becomes aware of an improvement only when the symptoms disappear. Some iron-deficient patients, with or without anemia, might have alopecia, atrophy of lingual papillae, or dry mouth due to loss of salivation. Other symptoms, such as weakness or digging fingernails (koilonychia), chlorosis, or the syndromes of Plummer-Vinson or Paterson-Kelly (dysphagia with esophageal membrane and atrophic glossitis) have virtually disappeared. These changes were caused by reduction of iron-containing enzymes in the epithelia and the gastrointestinal tract. Pica, the eating disorder in which there is an irresistible desire to lick or eat non-nutritive and unusual substances, such as soil, chalk, gypsum, ice (pagophagia) or paper, might appear in some cases. Pagophagia is considered quite specific to ID and it responds quickly to treatment. In a study on a group of patients referred to a gastroenterology consultation, more than half had pagophagia. It was especially frequent in women, and was not related to the cause of bleeding^[15].

Physical examination might be normal or show pallor of varying intensity, there may be a systolic murmur in cardiac auscultation, and abdominal and rectal exploration will allow us to rule out the existence of masses at those locations.

LABORATORY DIAGNOSIS: ID WITH OR WITHOUT ANEMIA

The diagnosis of anemia is simple and objective: the World Health Organization defines it as the decline in blood hemoglobin to a concentration below 13 g/dL in men and 12 g/dL in women. However, to confirm that ID is the origin of the anemia is not always easy. Sometimes the simple blood cell count strongly suggests this origin, the typical pattern being microcytosis, hypochromia (perhaps the most important, even more than the microcytosis), and elevation of red cells distribution width (RDW). However, up to 40% of

“pure” IDA cases are normocytic. Therefore, a normal mean corpuscular volume (MCV) does not exclude ID from being the cause of the anemia. Moreover, the presence of microcytosis does not necessarily imply ID and can be produced by other anemias (chronic process, sideroblastic anemia) and diseases (e.g. thalassemia). RDW measures the degree of anisocytosis (size difference) of the population of red cells and its elevation is neither sensitive nor specific for ID. The next step is to determine the so-called iron metabolism (in addition to all other necessary determinations, including levels of vitamin B12 and folic acid) and in many cases the level of C-reactive protein. A typical pattern is a decrease in sideremia, plasma ferritin, and transferrin saturation. However, this is not the usual case. The least reliable parameter for diagnosis of ID is probably the determination of sideremia, because it could be detected as an artefact of contamination of laboratory equipment, it has a nocturnal rhythm and it can normalize hours after ingestion. Serum ferritin, in the absence of inflammation (usually defined as a normal C-reactive protein level), reflects total body iron deposits. Thus, a low serum ferritin (< 30 ng/L) unequivocally means ID, whether accompanied by anemia or not. However, as serum ferritin is an acute phase reactant, a normal or even elevated ferritinemia does not exclude the presence of ID. Thus, in the presence of an inflammatory process (usually defined by an elevated C-reactive protein level), ID could exist even with levels of ferritin up to 100 ng/mL. Another parameter of the normal “iron metabolism”, especially useful when the determination of ferritin is equivocal, is the transferrin saturation index. This shows the percentage of transferrin that transports iron and thus a decrease (< 20%) implies ID, either absolute or functional.

In some cases, even taking into account all these determinations, ID can be difficult to diagnose. It generally occurs in situations where the anemia has a multifactorial origin. This is typical in cases of anemia of mixed origin, a chronic process that coexists with ID, which is a frequent scenario in gastrointestinal inflammatory disease or cancer. Even with all the determinations previously described, it can be difficult to estimate the role of each factor in the genesis of anemia in this setting. In these cases, other values can help us to assess the pathogenesis of anemia. These other factors include the determination of soluble transferrin receptor, reticulocyte hemoglobin concentration, the percentage of hypochromic red cells, the concentration of erythropoietin (and its relation to the expected values), and even the determination of hepcidin. The soluble transferrin receptor is one of the most useful as it is the least influenced by the presence of inflammation and it correlates well with concentration of transferrin receptor in the cell plasma membrane^[16]. If the levels are high, ID is likely to be a major component of anemia, while in those cases with normal or low levels; anemia is probably not associated with ID. In Table 2, the values of different determinations in different clinical scenarios are shown.

Table 2 Differences between the serum values of iron-deficiency anemia, anemia of chronic diseases, and anemia of mixed origin

	Iron-deficiency anemia	Anemia of chronic diseases	Anemia of mixed origin
Serum iron	Decreased	Decreased	Decreased
Transferrin	Increased	Decreased or normal	Decreased
Transferrin saturation	Decreased	Decreased	Decreased
Ferritin ¹	Decreased (< 30 ng/mL)	Increased (> 100 ng/mL)	Normal
Soluble transferrin receptor	Increased	Normal	Increased or normal
C-reactive protein	Normal	Increased	Increased
Erythropoietin	Increased	Normal or slightly increased for the degree of anemia	Increased or normal

¹Ferritin values between 30 and 100 ng/mL: Make other determinations to differentiate the two entities.

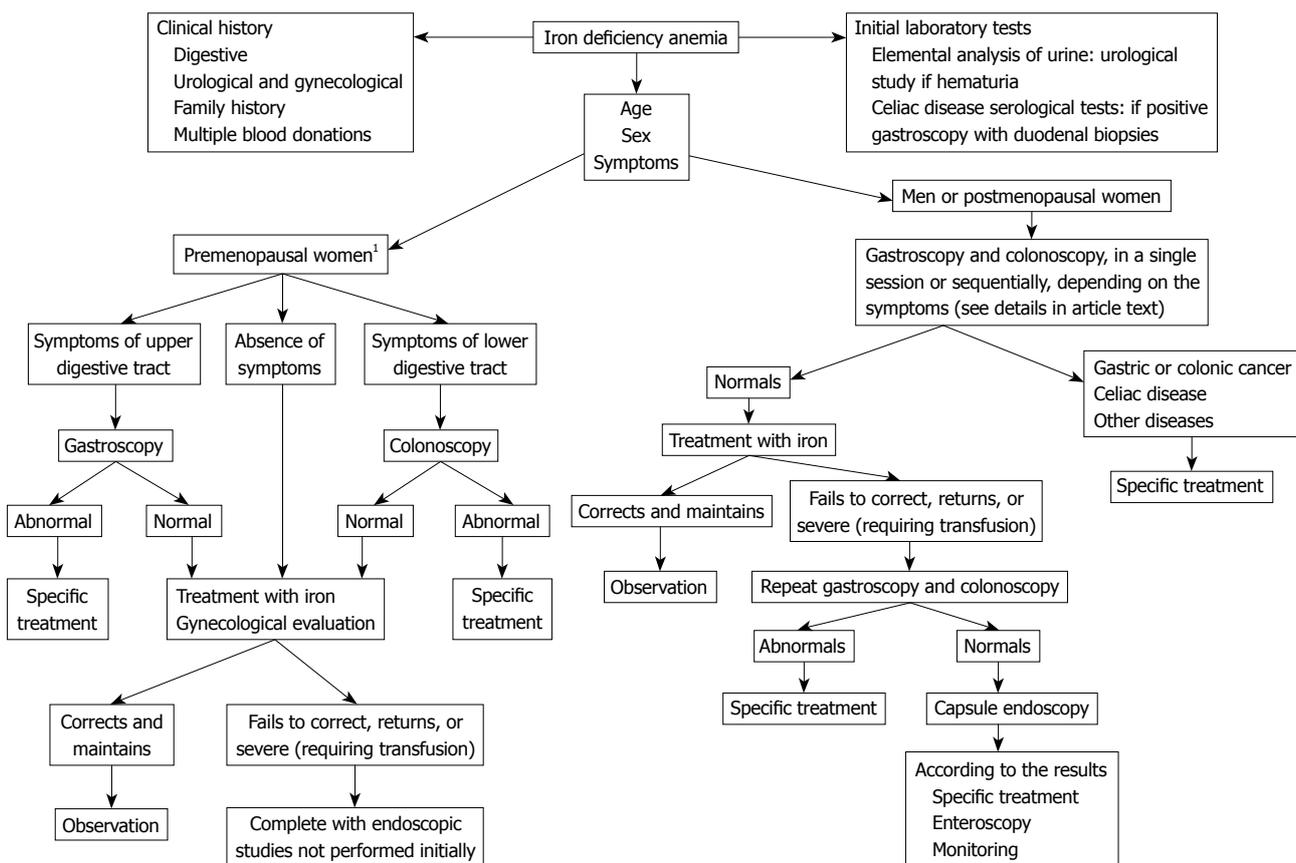


Figure 1 Etiologic diagnosis of iron deficiency anemia. ¹We must always consider gynecological cause.

ETIOLOGIC DIAGNOSIS OF ID ANEMIA

Once the diagnosis of IDA or ID without anemia has been established, it is necessary to investigate its origin (Figure 1), because it can be caused by very serious diseases. Taking into account the age and sex of the patient, and of course an adequate clinical history, we will plan a diagnostic strategy in every individual case.

In the clinical history, we should investigate any sign of digestive or urologic bleeding, and in the case of women, gynaecological history and symptoms should be included. Personal history of peptic ulcers and a family history of colon cancer or celiac disease should be investigated. The existence of suggestive symptoms in a location is a predictor of disease in that location. Therefore, the initial evaluation can be accompanied by the location of symptoms¹⁷.

The initial studies should include laboratory tests, with an elementary analysis of urine (up to one third of

the renal carcinomas have anemia). In the case of positive serological tests for celiac disease, it is also necessary to perform a gastroscopy with distal duodenum biopsies. In most patients, a dilemma will arise; is it necessary or mandatory to perform a gastroscopy, a colonoscopy or both? In patients over 50 years old, a colonoscopy is preferred to gastroscopy, and on the other hand, many of the patients under study for ID might have an indication of preventive colonoscopy screening, either because of family history or age (over 50 years)¹⁸. It has been described that in the presence of a low ferritin value, the probability of finding any pathology at colonoscopy will be quadrupled¹⁹. This supports the need for colonoscopy in the study of IDA and ID. It is important to underline that up to 15% of cases may have synchronous lesions in the upper and lower digestive tract, which means that it is necessary to perform both techniques, except in those cases in which celiac disease or a neoplasm is diagnosed

in the initial examination^[1]. Gastrointestinal endoscopies (gastroscopy and colonoscopy) might be performed in the same session or sequentially, according to clinical history (or serologic data). The combination of gastroscopy and colonoscopy is highly sensitive and specific for locating gastrointestinal lesions that produce anemia^[3,20,21]. However, the combination of both endoscopic techniques only determines the final cause of anemia in a little more than half of the patients. In a prospective study carried out on 100 consecutive patients with IDA, gastrointestinal endoscopies revealed at least one lesion potentially responsible for the loss of blood in 62 patients, 36% by gastroscopy, 25% by colonoscopy, and 1% by both^[17]. If examinations are normal, the anemia is not severe and symptoms do not suggest significant disease. The next step might be clinical follow-up, oral iron treatment (but iron supplementation may be harmful in some patients, e.g. in those with renal diseases) and cessation of any NSAIDs or aspirin consumption. Patients not responding to treatment with oral iron, those with severe anemia, or suspected serious illness, will require re-evaluation^[1,22]. Some authors describe that in the elderly, low MCV (≤ 60 fL) and a positive test for fecal occult blood are predictors of the presence of potentially bleeding lesions in endoscopy in patients with anemia without gastrointestinal symptoms^[23]. In premenopausal women, the most frequent endoscopic findings are gastritis by *H pylori* and celiac disease, and it has been suggested that in these patients initial diagnostic approach to IDA may include, in addition to the serologic celiac tests, a ¹³C-urea breath test, reserving endoscopic studies for cases where these tests are negative or anemia persists despite the eradication of *H pylori*^[24]. Finally, in the study of ID or IDA it must be pointed out that a barium enema is not a useful tool, being clearly inferior to colonoscopy^[25].

In those patients whose non-favourable clinical course after negative endoscopic studies advises further evaluation, repeating the endoscopic studies is justified because a proportion of lesions within the reach of conventional endoscopes might not be detected for several reasons. Repeating a gastroscopy might show erosions in a large hiatus hernia (Cameron lesions), peptic ulcer and vascular ectasy not detected in a previous exploration^[26]. Repeating a colonoscopy has a slightly lower yield, but it is a reasonable and necessary option if the previous colonoscopy was suboptimal because of incomplete or poor preparation. It has been shown that colonoscopy can fail in the diagnosis in 5% of colorectal tumors due to several reasons: an incomplete exploration, poor bowel preparation, misinterpretation of findings, inadequate biopsies of lesions^[27], or just not seeing the lesion.

In those cases in which repeated endoscopic examinations are all negative, we should investigate the small bowel as the source of anemia. In this scenario, the best initial approach is probably a capsule endoscopy^[28], reserving enteroscopy (single and double-balloon) for cases in which it is necessary to apply a treatment or to obtain biopsies of lesions localized by the capsule^[29,30]. This strategy significantly reduces the number of patients

requiring an alternative study after an initial investigation of the small intestine. Capsule endoscopy is a technique that explores the entire small intestine, something which is not always possible with enteroscopy. Capsule endoscopy has the disadvantage that it does not allow biopsies of detected lesions. The most common findings in patients with bleeding of obscure origin and/or IDA are angiodysplasia and Crohn's disease^[31]. According to the results of the meta-analysis of Triester *et al*^[32], diagnostic yield of capsule endoscopy (63%) in a study of patients with gastrointestinal bleeding of obscure origin was higher than that of push enteroscopy (26%), and of contrast studies with barium (8%). Enteroscopy should be considered as a second line technique in patients with a positive capsule endoscopy requiring sampling for histology or performing therapeutic endoscopy, and in patients in whom the suspicion of a small intestine lesion is high, despite the negativity of the capsule^[33].

Classical imaging studies of the small intestine (bowel through and enteroclysis) are much less sensitive for detecting lesions potentially causing anemia^[17] and have been reserved for those centres where the previous techniques are not available or are contraindicated. Radiological studies of the small bowel with computed tomography or magnetic resonance imaging techniques, which are very useful in the characterization of tumors from these locations and in the diagnosis of inflammatory bowel disease could, in experienced hands, increase the diagnostic yield^[34].

Finally, we should bear in mind that enteropathy by NSAIDs affects a significant number of people using these drugs, and that the amount of blood lost with the regular use of NSAIDs, such as ibuprofen, can be quite large^[35]. Injuries by the use of classic NSAIDs and selective inhibitors of COX-2 are very common (50%-70%) in the evaluation of the small intestine, i.e. by capsule endoscopy^[36,37]. We must remember that despite treatment with gastro-protective agents (proton pump inhibitors), aspirin and NSAIDs can cause gastrointestinal lesions of the lower bowel and thus cause bleeding and chronic ID.

CONCLUSION

IDA and ID are quite frequent in digestive pathology and they must always be taken into consideration for two reasons: (1) they have a clear impact on the patient's quality of life, and therefore they require adequate treatment and (2) they can be the consequence of significant or severe diseases, so it is essential to investigate their origin. Initial etiological evaluation must include celiac disease serological tests. In many patients, the usual endoscopic studies (gastroscopy and colonoscopy) will be prescribed, as they are necessary to rule out more severe diseases and they allow identification of the origin of anemia in more than half of the cases. In the rest of the patients, if anemia is severe or it does not respond to oral iron treatment, the first step will be to repeat those studies. If the results are still normal, it is necessary to investigate the existence of lesions in the small bowel by using capsule endoscopy. With all the diagnostic means

available nowadays, very few IDAs should be left without a diagnosis.

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