RESEARCH ARTICLE

Iron Deficiency in the Absence of Anemia - A Common, Complex and Challenging Disease to Treat

Esa Soppi, MD, PhD, adjunct professor, internal medicine[*,1]

[1]Viipurintie 96 C 1
20780 Kaarina, Finland

*esa.soppi@mitconsulting.fi

ABSTRACT

Iron deficiency in absence of anemia and blood count changes is a common disorder. Since iron is an essential cofactor not only of hemoglobin and myoglobin but also of numerous enzymes fundamental for many biological processes, it is understandable that the spectrum of iron deficiency related symptoms may be complex, severe and difficult to associate with iron deficiency. This often leads to significant diagnostic delays and a multitude of misleading diagnoses and treatments. Therefore, considering a diagnosis of iron deficiency without anemia requires a high degree of alertness. The second step in the diagnostic process, following consideration of the possibility of iron deficiency, is a careful history that covers all potential causes of deficient iron stores since the patient's birth and beyond combined by the appropriate investigations. The ferritin concentration is key for ascertaining the diagnosis. A ferritin concentration of less than 30 µg/L in a symptomatic individual means iron deficiency, but the patient may be iron deficient with much higher ferritin concentrations. Simultaneous determination of C-reactive protein with ferritin is practically useless. The treating physician should be familiar with the complexity of ferritin determinations and the interpretation of the results. The mainstay of treatment is oral iron but a considerable proportion of patients are intolerant or insufficiently responsive to oral iron and require intravenous iron therapy. The longer the duration of the iron deficiency, the more complicated the treatment and the patient's recovery may become. For some patients, iron deficiency seems to be a chronic disorder requiring management exceeding 5 years. In 1–5% of patients, particularly those with a duration of iron deficiency in absence of anemia of more than 15–25 years, the restoration of iron stores does not lead to clinical recovery within 5 years of follow-up. Iron deficiency without anemia has a high impact on the well-being and quality of life of the affected individuals and impacts significantly also on society, since the challenges in recognition, diagnosis and treatment of the condition generate costs probably in excess of 100 million euros/5 million inhabitants.

Introduction

Iron deficiency anemia affects more than 1,000 million individuals worldwide, and iron deficiency without anemia (IDWA) is even three times more frequent.[1] Clinical data is emerging showing that many patients may remain in prelatent or latent stages of iron deficiency without ever progressing to anemia[2-5] but still remaining symptomatic.

Iron or haem are essential parts or cofactors of the functionality of 100–200 enzymes, such as cytochromes, peroxidases including thyroid peroxidase, iron-sulphur proteins and metalloflavoproteins, aconitase, tyrosine reductase and tryptophan pyrrolase. These substances are fundamental for many biological processes in the body, including thyroid hormone production and action, oxygen transportation, DNA synthesis, mitochondrial respiration and energy production, myelin and neurotransmitter synthesis and metabolism. Therefore, iron deficiency can cause a multitude of symptoms which imitate many diseases and which vary from individual to individual.[3,4,6,7]

In the absence of anemia or typical changes in blood count, it may be very challenging to establish the correct diagnosis. Typical symptoms of IDWA include fatigue, brain fog, muscle and joint pains, weight gain, headache, dyspnea, palpitations, sometimes associated with sleep disturbances, arrhythmia, lump in the throat or difficulty in swallowing, or restless legs.[4] Over time, patients have often received a spectrum of diagnoses and, consequently, treatments, e.g., hypochondria, subclinical hypothyroidism, fibromyalgia, burnout, overtraining, asthma, mood changes extending from melancholy to severe therapy resistant depression, irritable bowel syndrome and attention deficit disorder. It is important to keep IDWA in mind as a differential diagnosis, because this type of iron deficiency is very often associated with symptoms that severely impair the patient's performance and quality of life and may even hinder the patient from overcoming the ordinary challenges of everyday life and even cause permanent disability.[2,4,5,7]

During my career as a consulting internist for more than three decades I have treated over 5,000 patients and cared personally for more than 2,000 iron infusions to patients with iron deficiency, of whom a significant part without anemia. Now I take the opportunity to share my experiences regarding the diagnosis and management of patients with iron deficiency in the absence of anemia.

Diagnosis of iron deficiency in the absence of anemia

Modern patient information systems provide data about hemoglobin, platelets and red cell indices over long periods of time and may disclose reduced values, albeit within the normal ranges. This may give a hint of iron deficiency or emergent iron deficiency. The spectrum of indicators for identifying different stages of iron deficiency is presented in Table 1.

Table 1. Indicators of different stages of iron deficiency

Indicator	Prelatent	Latent[#]	Preanemia[#]	Anemia
Hemoglobin	Normal	Normal	Often reduced but within the reference range	Reduced
Mean corpuscular volume/ mean corpuscular hemoglobin concentration	Normal	Normal but close to lower limit of reference	Slightly reduced	Unequivocally reduced
Symptoms	May exist	Common	Common and may be debilitating	Common including classical symptoms of anemia
History	Important	Important	Important	Important
Serum/plasma ferritin	Reduced	<50-70 µg/L	<30 µg/L	<10-15 µg/L
Transferrin saturation	Normal, $\geq$30%	Normal, 20–30%	15–20%	$\leq$15%
Soluble transferrin receptor in serum	Normal	Normal	Often increased	Increased
Serum hepcidin	Close to low of the highest quartile of the reference range	In the middle of the reference range	Close to high of the lowest quartile of the reference range	Close to low of the reference range
Bone marrow iron	Reduced	Reduced	Absent	Absent

A significant part of these patients may never progress to overt anemia

Symptoms

First and foremost, IDWA should be within the scope of recognition by treating physicians when considering the patient's symptoms. The wide spectrum of common symptoms is presented elsewhere,[3,4,6,7] but symptoms may be very peculiar, indeed (Table 2).[4] Iron deficiency affects many functions and tissues, e.g., skin and mucosal membranes which results in dry skin and eyes. In iron deficiency the iron absorption in the gastrointestinal tract is reduced,[6] so is the absorption of vitamins B12 and D. Lump in the throat, difficulties in swallowing, chest pain without reflux of acid, nausea, loss of appetite and symptoms of irritable bowel syndrome are not uncommon among patients with IDWA as a sign of mucosal membrane involvement but endoscopic changes are absent. The function of the endometrium is also affected and this results often in increased menstrual blood loss and, sometimes, in childlessness and recurrent miscarriages.

Patients with IDWA may have a history of years or even decades of severe iron deficiency and may still have remained rather asymptomatic. However, symptoms may surface rapidly after some stressful event (loss of a close relative, accident, surgery, severe disease such as pneumonia or covid-19 infection) and patients may become severely symptomatic and ill and lose their ability to work and even their ability to take care of themselves.

Table 2. Infrequent symptoms in non-anemic patients with iron deficiency

Less common	Rare
Exceptional fatigue lasting several days after mild to moderate physical activity	Numbness or dysesthesia (pins and needles) of the extremities on one side of face or body, which may require ruling out of multiple sclerosis
Severe headache and treatment-resistant migraine	
Severe memory lapses forcing the patient to take rigorous written notes of everything	Color vision disturbances and blurred vision/inability to focus
Symptoms start rapidly after a stressful event (losing close relative, accident, surgery, severe disease such as bacterial pneumonia or covid-19 disease)	Childlessness and recurrent miscarriages
	Objectively detected hot/burning skin without fever
Weight loss#	Severe heart rate disturbances leading even to syncope at rest or during exercise
Muscle tension and cramps unresponsive to muscle relaxants and massage	Hypokalemia, not associated with high blood pressure or hormonal changes and unresponsive to potassium substitution and spironolactone
Therapy-resistant heavy menstruation	
Snoring and sleep apnea, both of which resolve when iron deficiency is corrected	Tongue pain
	Urticaria
Inability to get sun tanning which is reversed when iron stores have been repleted	Severe sleeping disturbances / insomnia, which may lead to psychiatric care
Nausea and loss of appetite	Severe depression resistant to treatment including electroconvulsive therapy
Plantar fasciitis	
Bruxism	Transient swelling of joints without inflammation

About 10% of patients lose weight, 60% gain weight and in 30% the weight remains stable

Patient history and causes of iron deficiency

Secondly and essentially important, a careful patient history should be taken. The lifetime history should cover all potential causes of deficient iron stores since birth and even beyond[4] (Table 3) and supported by tests and examinations to reveal the underlying cause(s) and to rule out ongoing bleeding or decreased iron absorption.

A crucial part of history taking is to collect information, if possible, about the duration of the iron deficiency, since this impacts the complexity of managing the condition. If the patient has ever had anemia, she (he) must be considered to have been iron deficient since that time. Especially anemia of <100 g/L after delivery should be recorded, since recovery from the anemia often empties the patient's iron stores and symptoms emerge. It is important to collect information on the patient's siblings, since the younger the patient is compared to his/her siblings the more probable is iron deficiency, due to progressive maternal iron depletion during consecutive pregnancies. It is also important to collect information on the siblings as to whether they are or have been symptomatic and/or iron deficient.

Information is needed concerning the mother during all her pregnancies (anemia/symptoms) and the maternal siblings, including the maternal mother, if possible. When a diagnosis of iron deficiency of a female patient has been established and if she has children, the children should be examined. I have, over the years, treated several families where females have been iron deficient in up to four generations.

Table 3. The most common causes of iron deficiency

The four most common causes	Other common causes
Heavy menstruation any time in history	Ulcerative colitis, Crohn's and celiac disease
Pregnancy (multiple) and/or blood loss (> 500 mL) at delivery	Severe nose or occult intestinal bleedings (polyps, tumors, occasionally hemorrhoids)
Multiple blood donations	Achlorhydria or chronic use of proton pump inhibitors
Maternal iron deficiency during pregnancy leading to iron store depletion of the newborn	Previous anorexia and/or vegetarian diet of long duration
	Competitive athletics, such as track and field/skiers

Iron deficiency at birth due to maternal iron deficiency during pregnancy is the fourth common cause of iron deficiency (Table 3) but goes too often unrecognized. This may result in the development of anemia and/or symptoms within the first year of life. The second crucial point is at the age between 2 and 4 years after the period of rapid growth where the body consumes a lot of iron from the iron stores. The third crucial iron-depleting life event is puberty due to the growth spurt which in females is further exacerbated with the menarche. If anemia develops at these ages, a suspicion of iron deficiency from birth may arise. If the anemia goes unrecognized or insufficiently treated to ensure the full restoration of the iron stores, iron deficiency may go unrecognized even for decades. The patients' condition can vary from severe symptoms preventing them from managing school, studies or work to fairly asymptomatic or the patients may become symptomatic when faced with additional iron loss. Over time, patients typically undergo extensive medical examinations, the cost of which often exceeds 100,000 euros, and receive various diagnoses, such as presented in Table 4.

Table 4. Working diagnoses of patients who turned out to have iron deficiency in absence of anemia

Hypochondria
Subclinical hypothyroidism
Asthmatic symptoms (not fulfilling the diagnostic criteria)
Fibromyalgia
Depression
Irritable bowel syndrome / Gluten sensitivity without celiac disease
Attention deficit disorder
Marginally low testosterone (suspicion of male menopause)#
Patients with medically unexplained symptoms
Unexplained heart disease due to complex arrhythmia
Chronic Lyme disease
Chronic fatigue syndrome (CFS)
Long Covid syndrome

#Initiation of the testosterone treatment leads often to a rise in hemoglobin which reduces the existing iron stores and results in a fading testosterone effect and, ultimately, to a worsening of the patient's symptoms

The symptoms may be perceived as being so typical for hypothyroidism that thyroid medication is started, although only the thyroid stimulating hormone concentration may be slightly increased or even when the thyroid blood test results do not indicate any thyroid disease. Thyroid medication often leads to temporary symptom relief lasting for up to 6–12 months, after which the response subsides and the dose needs to be increased or T3-medication started, which will provide a new temporary response. Later on, with delayed diagnosis and prolonged thyroid hormone use, the clinical response to iron therapy may be inadequate, especially if the thyroid hormone dose has been increased to more than what corresponds to 100 ug levothyroxine for longer periods. Still, thyroid medication should not be stopped immediately when the correct diagnosis has been established since that would result in worsening of the patients' condition.[8] First, the T3 medication should be switched to levothyroxine and then an effort made to gradually wean the patient from levothyroxine.

Laboratory diagnosis
Ferritin should be used as the primary laboratory measure to detect iron deficiency.[9] Ferritin <30 µg/L in a symptomatic patient means iron deficiency. The patient may be iron deficient at ferritin blood concentrations up to 100 µg/L (no bone marrow iron)[10,11] and, if transferrin saturation is below 20%, even at higher ferritin values (100–300 µg/L).[12]

Determination neither of transferring receptor concentration nor hepcidin — a liver-derived hormone regulating iron absorption and turnover — are generally useful when the ferritin concentration is below 50–70 µg/L, as long as the hemoglobin concentration is not decreased.[13]

Determination bone marrow iron is an invasive procedure and not widely available for outpatients. This procedure should therefore be reserved for unclear cases, i.e., when the ferritin concentration is above 100 µg/L but symptoms and history support a diagnosis of iron deficiency.

Differential diagnosis

Other conditions and diseases behind the symptoms need to be taken into consideration, e.g., stress, excessive smoking and alcohol use, sedentary lifestyle, obesity and fatty liver, high blood pressure, sleep apnea, disturbed glucose and calcium homeostasis, excessive use of B6-vitamin, sleep deprivation, depression, low testosterone, covert malignancy, use of illegal drugs and side effects of medicines. These conditions can, of course, coexist with iron deficiency.

Iron deficiency affects the activity of thyroid peroxidase which may reduce thyroid hormone production and increase marginally thyroid stimulating hormone (TSH), which may result in misinterpretation of the role of the thyroid in the patient's symptomatology and initiation of thyroid medication.

Many patients with low D-vitamin levels (<50 nmol/L) have symptoms that resemble those of iron deficiency and practically all with a D-vitamin concentration <25 nmol/L have symptoms. D-vitamin has a multitude of functions in the body, including suppression of hepcidin expression[14] - the master regulator of iron homeostasis. Therefore, the vitamin D concentration should be determined when iron deficiency is detected. Likewise, vitamin B12 and folic acid should be determined, since they are essential for a multitude of functions of the body and may give symptoms if low. When there are any challenges to the patient's recovery, it is essential that the concentrations of folic acid, vitamin D and B12 concentrations are corrected, if below the reference range or low.

Treatment and follow-up

Oral iron is the first-line treatment for managing iron deficiency with or without anemia. A dose of $\geq$200 mg ferro iron (Fe^{2+}) in divided doses is usually sufficient.[1] A dose below 100 mg daily will rarely be effective, especially if the history of iron deficiency is long. The first control should usually take place after 2–3 months after start of iron treatment and should include registration of the patient's symptoms, a blood count and the serum ferritin concentration. The patient's condition should have began to improve and the ferritin concentration should have increased by about 2–5 µg/L per week of adequate iron therapy. The aim is a marked improvement of the patient's well-being and a ferritin concentration >100 µg/L after 6–12 months of follow-up. After discontinuation of oral iron therapy the patient should be followed at least for two years even if the root cause of the iron deficiency has been eliminated, since in significant number of patients have recurrent symptoms and iron deficiency.

If the patient does not tolerate a sufficient dose of oral iron or if oral iron does not result in recovery within one year, the following steps are in order: 1) reevaluation of the potential causes of iron deficiency, 2) reevaluation of the presence of other diseases or conditions that could explain the patient's symptoms, 3) changing the oral iron preparation, 4) a frank discussion with the patient regarding the patient's opinion of the duration and reason for iron deficiency (if this has not been done previously) and a discussion between the patient and physician of the physician's professional opinion, suspicion or conclusion of the situation and 5) opening the discussion with the patient of possibility to use intravenous iron.

The duration of iron deficiency is an important factor in foreseeing the outcome of iron therapy (Figure 1). Often it is possible to estimate the duration of iron deficiency by careful history taking but not always. The patient's contribution is of great value since he/she has interest in becoming cured and is a good "detective". Furthermore, at least in Finland there is often access to documentation from early childhood to pregnancies and maternal pregnancies. Interviewing the parents and relatives will provide important feedback. Nevertheless, all these efforts and a meticulous history taking may be totally unconclusive and conclusions on the duration of iron deficiency can only be drawn from how the patient's findings change during therapy (Patient 5).
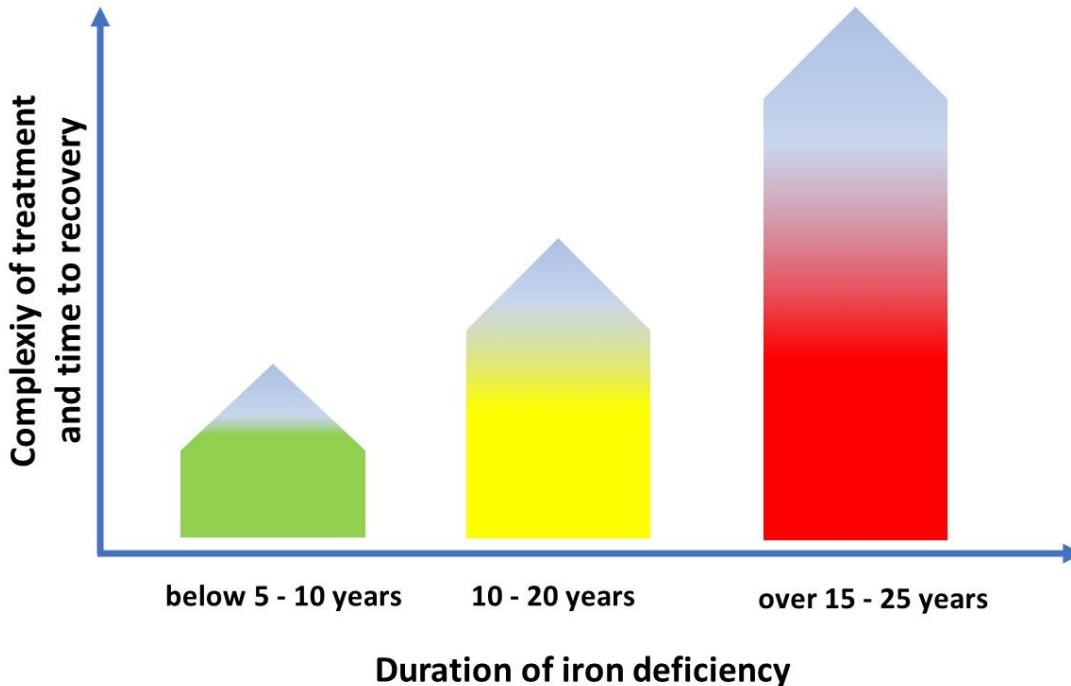
Figure 1. Schematic representation of the complexity and time to recovery as a function of the duration of iron deficiency without anemia. For patients with the first episode of anemia the duration of iron deficiency is usually less than 5–10 years.

Often the recovery of patients with and without anemia is rather straightforward and takes place within one year of oral iron administration or after one infusion (500 mg) of iron intravenously. I have used almost exclusively ferric carboxymaltose (FCM) and the usual dose is 500 mg/infusion. However, two thirds of patients need more than one infusion which may be repeated at the earliest after 6–9 weeks. When treating patients with iron deficiency anemia, correcting iron deficiency in women planning to become pregnant or treating pregnant women requires often a double dose (1000 mg). This dose induces a transient decrease of phosphorus in about half of the patients, but this decrease is rarely so severe as to cause symptoms. Adverse effects during iron infusions are rather rare and only about 1% of first infusions need to be terminated.[15] Adverse effects leading to the termination of subsequent infusions are very rare. During the week following the infusion it is not uncommon that the patient experiences mild joint and muscle pain, headache and fever usually <38°C for 2–3 days and moderate tiredness the duration of which varies. During the week following the iron infusion strenuous exercise should be avoided because it often leads to deterioration the patient's general condition. Later on, the symptoms of iron deficiency may markedly change, some may vanish, some may become worse and new symptoms may appear accompanied with prolonged tiredness which may be severe. The fluctuation of symptoms is accounted for by the effect of infused iron on changing iron homeostasis, since the severity of the symptoms seems to correlate with the duration of iron deficiency before treatment. These symptoms may be reduced or abrogated if the patient can take a course of oral iron before the infusion.

The signs that may indicate a longer duration of iron deficiency, the challenges in treatment and the need for longer periods of follow-up are presented in Table 5.

Table 5. Signs that may indicate a longer duration of iron deficiency and challenges in treatment

Oral iron	Intravenous iron
No or only a minor clinical response in spite of increasing ferritin levels Unproportionally high ferritin values in relation to iron dose and duration of therapy, often together with a high hepcidin concentration and persistent symptoms Significant weight gain (> 5–10 kg) within a few months (rare)	No or only a minor clinical response in spite of increasing ferritin levels Unproportionally high persisting ferritin values in relation to intravenous dose. This may take place especially after the second or third infusion, often in combination with a high hepcidin concentration and persistent symptoms Significant weight gain (>5–10 kg) within a few months after infusion (rather rare) Significant worsening of symptoms for weeks or months after the (first) infusion, especially of $\geq$ 1000 mg of iron

My experience has been that with increasing follow-up and repeated iron infusions the share of non-responders after 2000 or more infusions remains the same as after 1000 infusions, i.e., 3–4%, and those with a good or excellent response cover 78–80% of cases.[15]

Explanatory cases

Case 1. This female patient (age 27 years) came for a consultation because of tiredness, severe memory problems, difficulties of finding words to name objects, sleep disturbances, muscle cramps, joint and muscle pains and abdominal cramps of several years of duration. Eight years previously bone marrow aspiration had been performed because of thrombocytosis which proved to be reactive, since her bone marrow was devoid of stainable iron. Irritable bowel syndrome was diagnosed because of bowel cramps and persistent diarrhea and because a colonoscopy had been normal. Probably due to gastrointestinal symptoms no iron was prescribed, despite the bone marrow finding. Before the detection of absent iron stores she had donated blood nine times and after the detection she had still donated blood once. After menarche, she had had extremely abundant menstruations for 7 years, at which time she had started contraceptive pills which she had used without interruption for 20 years, during which time the menstruations occurred at 2–3 months' intervals. Based on the history I estimated that the duration of her iron deficiency was 10–15 years or more.

Her BMI was 21.3 kg/m^2 and the clinical status was normal. The hemoglobin concentration was 144 g/L with a normal blood count and ferritin was 23 µg/L. Oral iron (Fe^{2+}) (200 mg in divided doses) was prescribed (Figure 4). At first, the ferritin increased with improvement of the symptoms but at 8 months the patient's tolerance of oral iron faded and she continued on a dose of 100 µg every other day which resulted in a modest increase of ferritin concentration from 114 to 157 mg/L during the 8 months. During that time the symptoms started gradually to recur.

At 16 months hepcidin was determined and was low – 2.1 nmol/L (reference range 0.2-9.2 nmol/L). The patient was considered iron deficient, although the ferritin concentration was 157 µg/L, and an iron infusion was scheduled (Figure 2). This resulted in a good response[15] but gradually (between months 21–30) the patient's condition gradually deteriorated. Now hepcidin was in the midrange of the reference interval and a new iron infusion was administered. Now the response was only moderate, and within four months the patent became increasingly tired, dulled and anguished. Hepcidin was now close to the upper limit of the reference interval. The ferritin concentration remained now stable and a new visit was scheduled for clinical assessment and repeated testing of ferritin, hepcidin and the transferrin saturation.
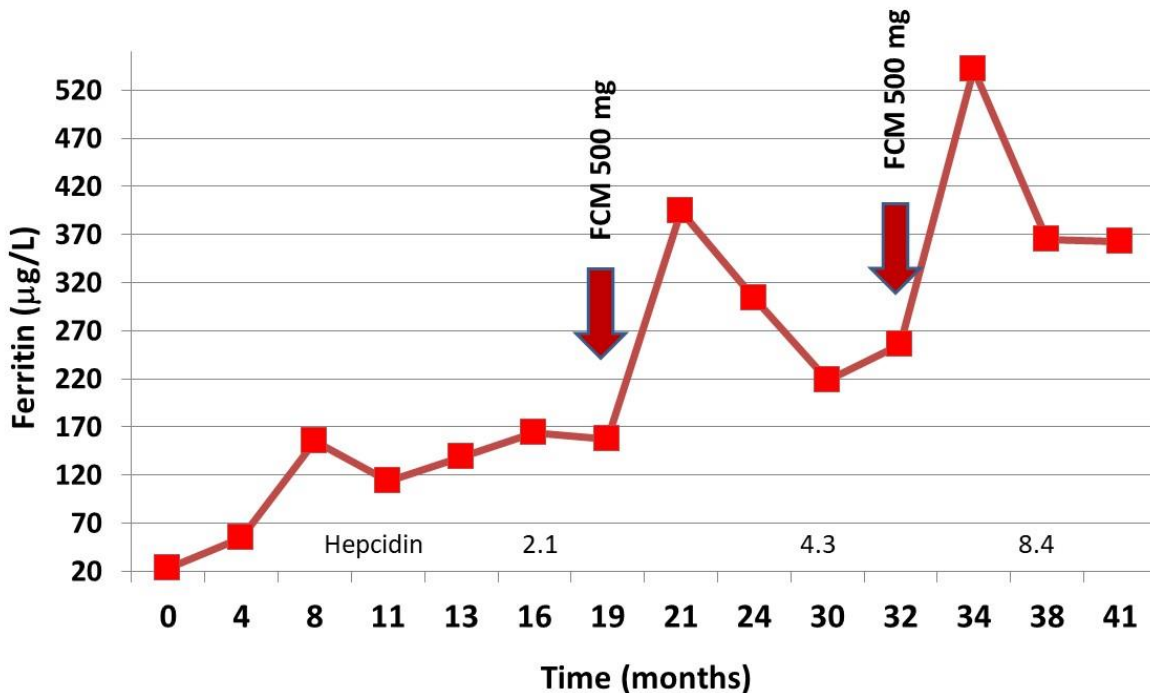
Figure 2. The patient's ferritin over the course of follow-up. FCM: ferric carboxymaltose
Interpretation. In the beginning the response to oral iron was as expected. The ferritin concentration remained stable on a rather high level, but was no reliable indicator of the patient's iron stores, as shown by the serum hepcidin level which indicated that the patient's iron deficiency was of long duration. Hepcidin was used as a means of assessing the patient's iron stores and for assessing the therapy with intravenous iron. The duration of her iron deficiency was reconsidered and the new estimate was 15–25 years or more.

Case 2. The patient had a long history of autoimmune thyroiditis but normal thyroid function test values. She had had one uncomplicated pregnancy 20 years previously when she was 29 years old. She had used a hormonal IUD since then and had no menstruation. Before her pregnancy menstruation had been scarce. She had no history of blood donations or other bleeding. She was the only child and her mother's pregnancy had been uneventful.

Three months before the visit the patient had started to experience severe tiredness and rapidly progressing dyspnea. At the time of the visit she was unable to speak while walking because of the dyspnea. Her body mass index was 21.2 kg/m² and the clinical status was normal with a blood pressure of 106/65 mmHg and a heart rate of 65/min. The blood count was normal with a hemoglobin of 141 g/L and tests for celiac disease, serum calcium and B12 vitamin normal, occult fecal blood was negative. Her ferritin was 36 µg/L. She was considered iron deficient without anemia, but the etiology and duration could not be established. Because of her severe symptoms intravenous iron was administered (Figure 3). After the infusion, the patient was totally symptom-free at a visit 5 weeks later and remained so for the next 5 years. Her hemoglobin remained at the same level during the follow-up and she had no obvious blood loss. At a visit 5 years after the iron infusion the patient reported tiredness and had a slightly increased TSH-value (4 mU/L), which is in the upper level of the reference range). Levothyroxine was prescribed. TSH fell to about 1 mU/L but her tiredness only increased during the next year.
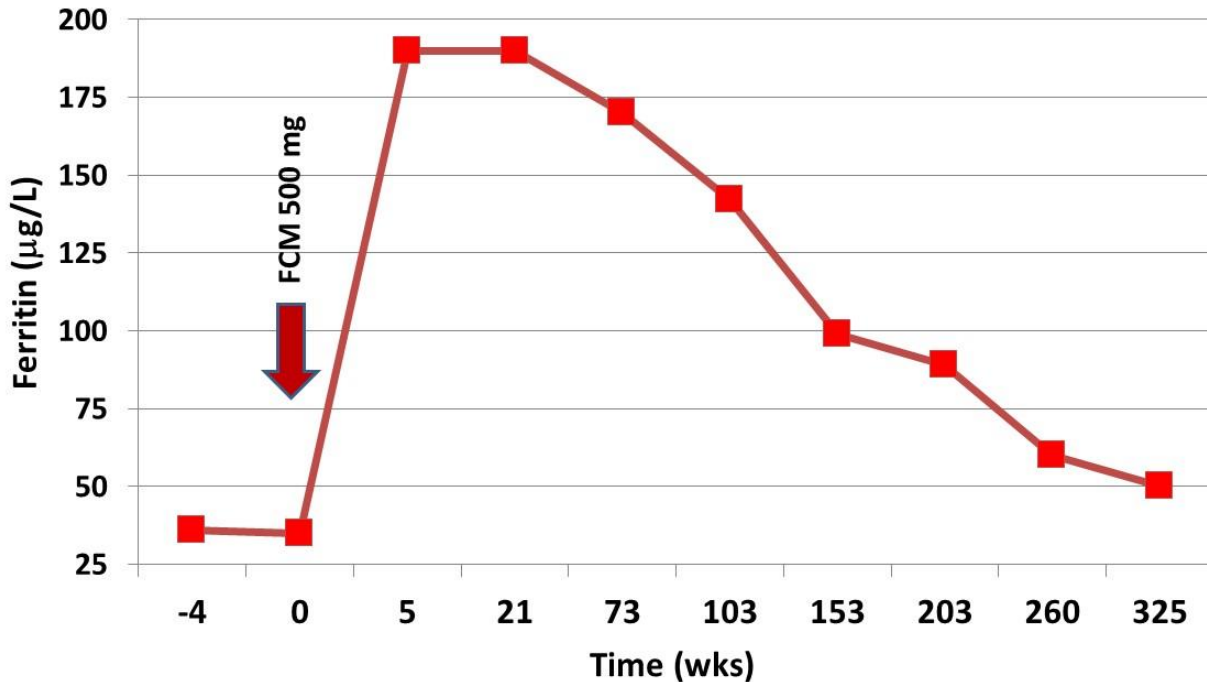
Figure 3. The patient's ferritin over the course of follow-up. FCM: ferric carboxymaltose
Interpretation. The patient had typical, severe symptoms of IDWA. Because of symptom severity the primary choice of therapy was intravenous iron and the outcome was excellent. Thereafter, the patient remained symptom-free for 5 years but she may still require more iron. The ferritin remained stable for 16 weeks after the iron infusion, after which it gradually decreased – a common finding in most of the patients. This was probably due to the utilization of the infused iron by the body. This patient shows how important long-term follow-up of IDWA is, despite an excellent primary outcome.

Case 3. This female patient (age 31) attended for a consultation because of severe tiredness, memory problems – so severe that she was unable to work – being cold, feeling exhausted and numbness of the upper extremities, dry skin, stomach pain and diarrhea. Because of the abdominal symptoms gastroscopy had recently been performed with normal findings which ruled out celiac disease. She had gained 5 kg of weight during the previous year. The symptoms had become much worse after a blood donation one year previously.

Levothyroxine had been prescribed a few months earlier because of the symptoms, although all the thyroid function tests had been normal. After initiation of levothyroxine the patient felt slightly better. At that time her hemoglobin had been 134 g/L and MCV 83 fL.

Her BMI was 26.8 kg/m^2 and the clinical status was normal. Her ferritin concentration was 29 µg/L. She reported that her younger sister had been anemic in early childhood and that her mother had had a low hemoglobin value during both pregnancies. The patient had thus been iron deficient from birth but had no anemia.

Oral iron (Fe^{2+}) (200 mg in divided doses) was prescribed but she was able to take this dose only for a few months due to gastric adverse effects and the ferritin concentration had risen only to 55 µg/L. Because of her severe symptoms four iron infusions were administered within 9 months (Figure 4). Her condition improved after the first three infusions, but after the fourth it deteriorated somewhat although the ferritin value and transferrin saturation percentage increased. She was negative for hereditary hemochromatosis. Thereafter she was carefully monitored and gradually her condition improved while both her ferritin and transferrin saturation declined. The improvement continued for three years by which time the ferritin concentration had considerably decreased and transferrin saturation was below 20%. The serum hepcidin concentration was now clearly below the upper limit of the reference range. The patient received the 5th iron infusion and her condition improved.
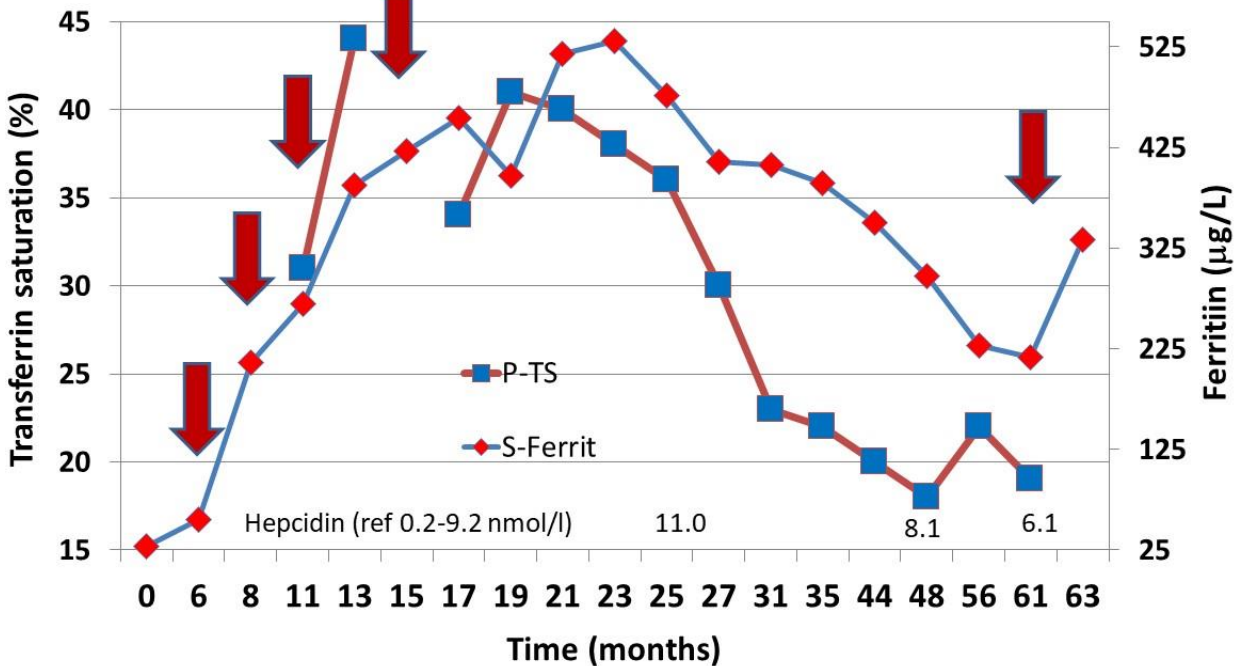
Figure 4. The patient's ferritin, transferrin saturation and hepcidin over the course of follow-up. Each red arrow indicates administration of 500 mg of ferric carboxymaltose (FCM) intravenously.
Interpretation. Oral iron failed because the patient did not tolerate the oral preparations. Due to severe symptoms (work disability) intravenous iron was used. The family history was elucidated only then. The administration of iron intravenously resulted in a high ferritin level but the transferrin saturation percentage increased only moderately. At the same time the serum hepcidin level was high, and these observations together may indicate that the patient's body was unable to utilize the infused iron. Thereafter the ferritin and hepcidin concentrations as well as transferrin saturation gradually decreased over three years time with reemergent symptoms. Improvement followed with an additional dose of intravenous iron.

Deciphering summary

IDWA is two to three times more common than iron deficiency anemia[1] and should be taken seriously.[4,5,16] As iron deficiency is progressing it may affect the tissue iron compounds unevenly in a way that cannot be predicted from the status of iron stores. Iron deficiency depends on the pace of drainage of iron stores, the severity of the deficiency and on the duration of the iron deficiency. This may result in depletion of iron-containing compounds from the tissues, including 100–200 enzymes that are fundamental for many fundamental biological processes in the body. Since long-lasting iron deficiency or iron deficiency from birth in the absence of anemia seems to be difficult to treat, recovery of iron stores and clinical recovery may require months or even years of follow-up and treatment. This being the case, one may ask if the genes encoding the enzyme proteins and/or proteins regulating iron uptake, iron recycling and iron storage are affected. Indeed, maybe gene activation and the recovery of protein functions are in poor balance which could explain why recovery is often associated with rapidly fluctuating symptoms and even new symptoms.

It is reasonable to expect enzymes located in the mitochondria and endoplasmic reticulum to contribute to the multitude of clinical manifestations affecting skeletal muscle and heart, central nervous and immune systems, thyroid, liver and gastrointestinal tract.[3,6,17,18] This corresponds well with the clinical findings of varying and numerous symptoms the patients often have.[4,8,19-21] There are some symptom-based diagnoses that resemble those of iron deficiency, e.g., gluten sensitivity without celiac disease/irritable bowel syndrome,[22] patients with medically unexplained symptoms,[23] functional neurological disorders,[24] chronic Lyme disease, chronic fatigue syndrome[7,25] and long covid syndrome, not to forget a number of patients with diagnoses of that kind that I have cured with iron therapy.

Ferritin is at the core of assessment of iron deficiency, although the suggested cut-offs for low and high ferritin concentrations vary.[9,26,27] Clinicians should be aware of the pitfalls when interpretating ferritin values. Information on the level of serum

ferritin should in certain cases be complemented with information on the transferrin saturation percentage and the serum hepcidin concentration, and, if available, an examination of a bone marrow aspirate for bone marrow iron. It is, nevertheless, important to understand that ferritin cannot and does not predict the status or balance of tissue iron. Indeed, the patient may be iron deficient despite stainable iron in the bone marrow and despite high ferritin values of 100–300 µg/L, if the transferrin saturation is below 20%.[12] Transferrin saturation is considered to be the most sensitive determinant of changes in the amount of iron due to from internal and external causes, since inflammations reduce serum iron and raise the transferrin saturation percentage.[3] Of note, patients with hereditary hemochromatosis can also become iron deficient. After repletion of iron stores, ferritin concentration is high, but if combined with an increased transferrin saturation testing for hemochromatosis is indicated (Case 3).

The ferritin concentration in the serum can increase markedly in infections and inflammatory conditions. Here, the CRP or ESR values are usually useless (they may not rise very much) and the reliability of the ferritin value rests on clinical judgement (Case 3). The most common cause of a falsely high ferritin value is fatty liver with inflammation, and this does not necessarily involve elevation of liver enzyme values; the CRP is practically always normal. Other cases where ferritin is usually temporarily increased for 2–4 weeks or more include major surgery, especially joint replacement surgery, tissue hematoma, delivery trauma, hyperthyroidism, covid vaccination and covid 19 infection, which may be quite mild.

Serum and plasma ferritin determinations should give similar results but when commercial kits are used, especially high concentrations (>100 µg/L) of ferritin may result in different values for serum and plasma ferritin. In cases where ferritin increases unproportionally in relation to administered iron dose or in relation to (poor) symptom relief, this may be due to a change in the molecular structure of ferritin, which is a complex molecule. Here, determination of serum hepcidin is especially helpful during intravenous iron therapy, when ferritin increases unproportionally and remains high. If the patient has liver involvement, hepcidin determinations are often unreliable. When large doses of iron are administered, typically intravenously, iron homeostasis may be disturbed or access of iron to the tissues restricted,[28] while patients are still symptomatic. Here, low hepcidin values may indicate iron deficiency and can be used to direct further therapy (Cases 1,3).[29,30]

Although ferritin and hepcidin concentrations are considered to correlate rather well,[28] the correlation coefficient, in my hands, is at best 0.5.[31] In situations where both ferritin and hepcidin are high but patients are symptomatic probably imply that iron is sequestrated to macrophages.[30] The hypothesis is that the body may feel that there is iron, but that it is not in correct place(s), i.e., not in the proteins which need iron to function properly. Often both (or preferably hepcidin) will decrease/increase first accompanied with symptom relief/worsening, probably influenced by the sequestration of iron (Cases 1,3). In these instances, the correlation of ferritin and hepcidin concentrations will be poor.

The most important goal of iron therapy is improvement of the patients' condition. About 80% of the patients will eventually respond well or excellently to oral as well as intravenous iron administration.[15] A small proportion of patients (1–5%) does not seem to respond to iron at all, not even after several years of follow-up. Usually the cause lies in a protracted duration of iron deficiency of 15–25 years or more. Chronic, untreated iron deficiency - a common disorder - may cause permanent damage where iron administration may have only a limited effect.[32,33] Ferritin should be followed periodically during the therapy, but ferritin is not the primary treatment target (Case 2). Usually, clinical response is achieved within one year of therapy and the ferritin concentration is then often > 100 µg/L but higher values are not rare. This is to be expected, since when the bone marrow iron stores are abundant, the ferritin concentration is often 200–300 µg/L.[10]

Iron deficiency with and without anemia are probably different entities of the same disease. IDWA is a chronic, and probably complex group of diseases which often go undetected for long periods of time, since IDWA is seldom considered as the primary or only cause of a patient's symptoms. The existence of IDWA is even denied. What is not known is why anemia does not develop even in people who may be severely iron deficient. Also, the pathophysiology of the symptoms and of the fluctuating recovery from the symptoms is based on limited evidence. I have provided some explanations in this paper. Hopefully, these thoughts will inspire future research to improve the management and care of patients with iron deficiency.

Conclusions

Iron deficiency in absence of anemia is common and complex condition which often goes unrecognized for longer periods. The path to diagnosis is high

alertness of suspicion of iron deficiency behind the symptoms, careful history of potential causes of reduced iron stores and ferritin determination. Often the iron deficiency in absence of anemia is chronic condition where recovery requires extended patience from all parties. This review consists of many findings that have thus far never been presented in the literature. The pathophysiology of the findings are in many cases unclear but explanations and hypotheses are provided based on available scientific data and deductive reasoning. I hope that this review is functioning as a sparkle of inspiration for future research.

Conflict of interest
None

References

1. Camaschella C. Iron deficiency. *Blood.* 2019;133(1):30-39. doi.org/10.1182/blood-2018-05-815944

2. Al-Jafar HA. HWA: Hypoferritinemia without anemia a hidden hematology disorder. *J Family Med Prim Care.* 2017;6(1):69-72. doi.10.4103/2249-4863.214986

3. Goodnough LT, Nemeth E. Iron deficiency and related disorders. 615-643. Greer JP, Arber DA, Glader BE, List AF, Means RT, Rodgers GM (eds). In *Wintrobe's Clinical Hematology*, 14th edition. Wolters Kluwer Health. 2018.

4. Soppi E. Iron deficiency without anemia – common, important, neglected. *Clin Case Rep Rev.* 2019;5(1):1-7. doi.10.15761/CCRR.1000456

5. Al-Naseem A, Sallam, A, Shamim Choudhury S, Thachil J. Iron deficiency without anaemia: a diagnosis that matters. *Clin Med. (Lond)* 2021;21(2):107–113. doi.10.7861/clinmed.2020-0582

6. Dallman, PR, Beutler E, Finch CA. Effects of iron deficiency exclusive of anaemia. *Br J Haematol.* 1978;40(2):179-184. doi.10.1111/j.1365-2141.1978.tb03655.x

7. Soppi E. Iron deficiency without anaemia - a clinical challenge. *Clinical Case Rep   .* 2018;6(6):1082–1086. doi.10.1002/ccr3.1529.

8. Ravanbod M, Asadipooya K, Kalantarhormozi M, Nabipour I, Omrani GR. Treatment of iron-deficiency anemia in patients with subclinical hypothyroidism. *Am J Med.* 2013;126(5):420-424. doi.10.1016/j.amjmed.2012.12.009

9. Camaschella C. Iron-deficiency anemia. *N Engl J Med.* 2015;372(19):1832-1843. doi.10.1056/NEJMra1401038

10. Harju E, Pakarinen A, Larmi T. A comparison between serum ferritin concentration and the amount of bone marrow stainable iron. *Scand J Clin Lab Invest.* 1984;44(6): 555–556. doi.10.1080/00365518409083610

11. Mast AE, Blinder MA, Gronowski, AM, Chumley C, Scott M. Clinical utility of the soluble transferrin receptor and comparison with serum ferritin in several populations. *Clin Chem.* 1998;44(1):45–51.

12. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Helmut Drexler H, Thomas F. Lüscher, TF, Bart B, Banasiak W, Niegowska J, Kirwan B-A, Mori C, et al., for the FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med.* 2019;361(25):2436-2448. doi.10.1056/NEJMoa0908355

13. Galetti V, Stoffel NU, Sieber C, Zeder C, Diego Moretti D, Zimmermann MB. Threshold ferritin and hepcidin concentrations indicating early iron deficiency in young women based on upregulation of iron absorption. *EClinicalMedicine.* 2021;39:101052. doi.10.1016/j.eclinm.2021.101052

14. Moran-Lev H, Weisman Y, Cohen S, Deutsch V, Cipok M, Bondar E, Lubetzky R, Mandel D. The interrelationship between hepcidin, vitamin D, and anemia in children with acute infectious disease. *Pediatr Res.* 2018;84(1):62–65. doi.10.1038/s41390-018-0005-0

15. Soppi E. Intravenous iron – personal experience of 1000 consecutive infusions. *Clin Case Rep Rev.* 2020;6(1):1-6. doi.10.15761/CCRR.1000492

16. Castelo-Branco C, Quintas L. Iron deficiency without anemia: indications for treatment. *Gynecol Repro Endocrinol Metabol.* 2020;1(4):215-222. doi.org/10.53260/GREM.201043

17. Paul BT, Manz DH, Torti FM, Torti SV. Mitochondria and iron: Current questions. *Expert Rev Hematol.* 2017;10(1):65–79. doi.10.1080/17474086.2016.1268047

18. Rineau E, Gueguen N, Procaccio V, Geneviève F, Reynier P, Henrion D, Lasocki S. Iron deficiency without anemia decreases physical endurance and mitochondrial complex I activity of oxidative skeletal muscle in the mouse. *Nutrients.* 2021;13(4):1056-1065. doi.10.3390/nu13041056.

19. Bener A, Kamal M, Bener HZ, Bhugra D. Higher prevalence of iron deficiency as strong predictor of attention deficit hyperactivity disorder in children. *Ann Med Health Sci Res.* 2014;4(3):291-297. doi.10.4103/2141-9248.141974

20. Murray-Kolb LE, Beard JL. Iron deficiency and child and maternal health. *Am J Clin Nutr.* 2009;89(suppl):946S–50S. doi.10.3945/ajcn.2008.26692D

21. Yao W-C, Chen H-J, Leong K-H, Chang K-L, Wang Y-T T, Wu L-C, Tung P-Y, Kuo C-F, Lin C-C, Tsai S-Y. The risk of fibromyalgia in patients with iron deficiency anemia: a nationwide population-based cohort study. *Sci Rep.* 2021;11:10496-10513. doi.10.1038/s41598-021-89842-9

22. Catassi C, Alaedini A, Bojarski C, Bonaz B, Bouma G, Carroccio A, Castillejo G, De Magistris L, Dieterich W, Di Liberto D, Elli L, Fasano A, Hadjivassiliou M, Kurien M, Lionetti E, Mulder CJ, Rostami K, Sapone A, Scherf K, Schuppan D, Trott N, Volta U, Zevallos V, Zopf Y, Sanders DS. The Overlapping area of non-celiac gluten sensitivity (NCGS) and wheat-sensitive irritable bowel syndrome (IBS): An update. *Nutrients.* 2017;9(11):1268-1273. doi.10.3390/nu9111268

23. Burton C, Fink P, Henningsen P, Löwe B, Rief W, on behalf of the EURONET-SOMA Group. Functional somatic disorders: discussion paper for a new common classification for research and clinical use. *BMC Medicine*. 2020;18:34-40. doi.10.1186/s12916-020-1505

24. Aybek S, Perez DL. Diagnosis and management of functional neurological disorder. *BMJ*. 2022;376:o64-o73. doi.10.1136/bmj.o64

25. Komaroff AL. Advances in understanding the pathophysiology of chronic fatigue syndrome. *JAMA*. 2019;322(6):499-500. doi.10.1001/jama.2019.831

26. Sezgin G, Monagle P, Loh TP, Ignjatovic V, Hoq M, Pearce C, McLeod A; Westbrook J, Li L, Georgiou A. Clinical thresholds for diagnosing iron deficiency: comparison of functional assessment of serum ferritin to population-based centiles. *Sci Rep*. 2020;10:18233-18244. doi.10.1038/s41598-020-75435-5

27. Fletcher A, Forbes A, Svenson N, Thomas DW, on behalf of and A British Society for Haematology Good Practice Paper. Guideline for the laboratory diagnosis of iron deficiency in adults (excluding pregnancy) and children. *Br J Haematol*. 2022;196(3):523–529. doi.10.1111/bjh.17900

28. Camaschella C, Nai A, Silvestri L. Iron metabolism and iron disorders revisited in the hepcidin era. *Haematologica*. 2020;105(2):260-272. doi.10.3324/haematol.2019.232124

29. Pasricha S-R, McQuilten Z, Westerman M, Keller A, Nemeth E, Ganz T, Wood E. Serum hepcidin as a diagnostic test of iron deficiency in premenopausal female blood donors. *Haematologica*. 2011;96(8):1099–1105. doi.10.3324/haematol.2010.037960

30. Litton E, Baker S, Erber W, Farmer S, FerrierJ, French C, Gummer J, Hawkins D, Alisa Higgins A, Hofmann A, De Keulenaer B, McMorrow J, Olynyk JK, Richards T, Towler S, Trengove R, Webb S, on behalf of the IRONMAN Study investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Hepcidin predicts response to IV iron therapy in patients admitted to the intensive care unit: a nested cohort study. *J Intens Care*. 2018;6(1):60-66. doi.org/10.1186/s40560-018-0328-2

31. Soppi E. Iron is hard stuff. A book in Finnish, 193 pages. *M.I.T. Consulting Ltd*. 2020.

32. Lozoff B, Smith JB, Kaciroti N, Clark KM, Guevara S, Jimenez E. Functional significance of early-life iron deficiency: outcomes at 25 years. *J Pediatr*. 2013;163(5):1260-1266. doi.10.1016/j.jpeds.2013.05.015

33. Stabell N, Averina M, Flægstad T. Chronic iron deficiency and anaemia were highly prevalent in a population-based longitudinal study among adolescent girls. *Acta Paediatrica*. 2021;110(10):2842–2849. doi.10.1111/apa.16016