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Hyperferritinemia and hypoferritinemia in the context of chronic fatigue syndrome pathogenesis: a literature review and clinical implications

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Abstract
Chronic fatigue syndrome (ME/CFS) is a multifactorial, exhaustive disease entity of unclear aetiopathogenesis, the main symptom of which is prolonged, unexplained fatigue that significantly limits daily functioning. Increasing evidence suggests a link between iron metabolism, particularly ferritin levels, and the occurrence of fatigue symptoms, even in the absence of anaemia. Iron deficiency can lead to mitochondrial dysfunction, reduced energy production, cognitive decline and reduced physical performance. In patients with ME/CFS, iron supplementation, especially with ferritin ≤15 ng/ml, can result in a marked improvement in symptoms, regardless of haemoglobin levels. At the same time, studies in the post-COVID-19 syndrome patient population point to the phenomenon of hyperferritinaemia, which may be related to chronic immune system activation, endocrine disorders and increased oxidative stress. Elevated ferritin levels in this group may act not only as an inflammatory indicator, but also as an active element in the pathogenesis of chronic fatigue. A possible correlation of ferritin with increased depressive symptoms and decreased IGF-I has also been established. In light of the current data, ferritin may be an available and useful biomarker to aid in the diagnosis and differentiation of ME/CFS, both in its classic form and in the course of long COVID. However, further studies are needed to validate its diagnostic, prognostic and potentially therapeutic role.

Keywords: ferritin, chronic fatigue syndrome, post - COVID syndrome, iron deficiency

1.Introduction

Chronic fatigue syndrome (ME/CFS) is a multifactorial disease entity characterised by prolonged, unexplained fatigue that does not resolve after rest and significantly limits the patient's daily functioning. The condition is estimated to affect between 0.2% and 0.4% of the population, more often women, often leading to a permanent impairment of quality of life [1]. Various terms for this entity are used in the literature, including myalgic encephalomyelitis (ME), chronic fatigue syndrome (CFS) and systemic exertion intolerance disease [2]. The aetiopathogenesis of ME/CFS has not yet been clearly established. It is thought that a variety of factors may play a role in its development, such as viral infections, immunological disorders, metabolic abnormalities and neuroendocrine dysregulation [3]. The disease is characterised by considerable clinical heterogeneity and its diagnosis, in the absence of specific laboratory tests, is based mainly on the history and clinical picture after excluding other possible causes. According to the current recommendations of the International Consensus Criteria (ME-ICC), the presence of the following symptoms for at least six months is necessary for diagnosis:

- Persistent, unexplained fatigue that does not subside despite rest and leads to a significant reduction in activities of daily living.
- Post-exertional malaise (PEM), defined as a worsening of symptoms after minimal physical or mental exertion.
- Cognitive disorders (brain fog), such as difficulties with concentration, information processing or short-term memory.
- Sleep disturbances, including sleep that is not restful.
- Often also complaints of pain (muscle pain, joint pain, headaches), hypersensitivity to stimuli, dysautonomic or flu-like symptoms [1]

PEM is considered one of the most characteristic symptoms of ME/CFS and allows differentiation with other causes of fatigue [4]. In addition to ME-ICC, other diagnostic criteria are used, including CDC/Fukuda, Canadian, Oxford and IOM/NAM, which vary in the range of symptoms required and restrictiveness, making it difficult to standardise diagnoses [5]. Many patients also present with symptoms suggestive of autonomic and immune system involvement, such as orthostatic intolerance, hypersensitivity to light and sound, gastrointestinal disturbances or flu-like symptoms [2].

In the absence of clear diagnostic biomarkers, research into metabolic and inflammatory markers is receiving increasing attention. In this context, ferritin, an iron storage protein and acute phase marker, is of particular interest as a potential biomarker of ME/CFS. Data to date suggest both the possible impact of low ferritin levels (latent iron deficiency without anaemia) and the role of hyperferritinaemia in the course of ME/CFS, particularly in the context of post-COVID-19 syndrome, further broadening the spectrum of potential pathogenetic mechanisms of this disease entity.

2. Ferritin deficiency - clinical and diagnostic aspects

2.1 Physiology of iron and ferritin in the body

Ferritin is the primary iron storage protein in the body, occurring both in the cytosol and plasma, where it reflects the body's iron stores and acts as a heme buffer of Fe^{3+}/Fe^{2+}, protecting cells from oxidative stress [6]. Iron plays an essential role in ATP synthesis as a cofactor of iron-sulphur centres in mitochondrial respiratory chain complexes, enabling efficient electron transfer and energy production. Its deficiency leads to destabilisation of these structures, impaired function of complexes I and III and reduced efficiency of oxidative phosphorylation. This results in a decrease in ATP production, increased oxidative stress and mitochondrial dysfunction, particularly in tissues with high energy requirements, such as brain and skeletal muscle [7]. In the nervous system, iron is an essential cofactor of tyrosine hydroxylase and tryptophan hydroxylase - enzymes crucial for the synthesis of neurotransmitters such as dopamine, noradrenaline and serotonin. Iron deficiency leads to a decrease in the activity of these enzymes, resulting in reduced production of monoamines, impaired neurotransmission and depressive and cognitive symptoms. In addition, reduced iron bioavailability in the brain can exacerbate oxidative stress and neurochemical imbalance, which affects central nervous system function [8]. Iron is a key factor for oligodendrocytes during myelination. This element acts as a cofactor for enzymes synthesising lipids and cholesterol, which are the main building blocks of myelin sheaths, and also determines their intensive ATP metabolism. In addition, its deficiency impairs neurogenesis and leads to structural changes in the hippocampus, such as impaired dendrite development and synaptic plasticity, which can result in permanent cognitive impairment. Finally, iron also promotes the stability and integrity of synapses, and iron deficiency results in a deterioration of the structure of synapses, which translates into reduced efficiency of neuronal transmission [9]. Disorders of iron homeostasis, even with normal haemoglobin values, can cause a range of neurological symptoms, including chronic fatigue, psychomotor slowing, impaired concentration, impaired working and episodic memory, and anxiety and irritability. These symptoms are due to insufficient iron supply to structures with high metabolic demand, such as the central nervous system, affecting both mitochondrial and synaptic functions.

The authors emphasise that these deficiencies can occur in spite of the absence of anaemia and should be considered in the differentiation of neuropsychiatric-type symptoms. Even subclinical iron deficiency affects neuronal metabolism, reducing the efficiency of cognitive function by impairing mitochondrial processes and neurotransmission. Therefore, already with ferritin levels below 30 ng/ml, regardless of the presence of anaemia, a neurological and cognitive assessment of the patient is recommended [10].

2.2 Symptoms of iron deficiency with normal haemoglobin (so-called latent iron deficiency)

Latent iron deficiency, despite normal haemoglobin levels, can cause a set of clinically significant symptoms that often go unnoticed or underestimated in daily practice. Chronic fatigue, often described as unexplained and unremitting despite rest, is one of the most common signals of iron deficiency in non-anaemic patients. This symptom usually co-occurs with weakness, lack of vitality and reduced exercise tolerance, which translates into difficulties in performing both work activities and daily duties [11]. Latent iron deficiency, characterised by normal haemoglobin levels, can cause a number of bothersome symptoms that significantly reduce patients' quality of life. One of the most commonly reported symptoms is chronic, increasing fatigue that does not subside after rest and limits the ability to perform daily activities. This fatigue is often associated with feelings of general weakness and lack of energy, which can impede both physical and intellectual work [10]. Somatically, there is a weakness of muscle strength, which manifests itself not only during intense exertion, but also in everyday activities such as climbing stairs or taking a long walk. The impairment of muscle function is due to a limited supply of iron, which is necessary for the proper functioning of the mitochondria, but from the patient's point of view this manifests itself mainly as rapid fatigue and a feeling of lack of strength [11]. Also among the frequently reported symptoms is excessive hair loss, which is due to impaired proliferation of hair follicle cells. Hair loss, especially when it is severe and prolonged, can affect patients' mood and psychological well-being [12]. Some patients also develop skin symptoms such as pallor or dry skin, although these are usually not predominant. In the absence of features of overt anaemia, symptoms of latent iron deficiency are sometimes downplayed or attributed to other causes, leading to delayed diagnosis. Consequently, despite the significant impact on daily functioning, iron deficiency remains undiagnosed and patients do not receive adequate therapeutic support [13].

Table 1. Physiological functions of iron and the effects of iron deficiency in the context of chronic fatigue. Own elaboration based on the literature.

The function of iron in the body	Consequences of Deficiency	Clinical Symptoms	Sources
Participation in ATP synthesis (mitochondrial complexes I and III)	Decreased energy production, oxidative stress, mitochondrial dysfunction	Chronic fatigue, weakness, limited exercise tolerance	[7,14]
Role in neurotransmitter synthesis (dopamine, serotonin, norepinephrine)	Reduced monoamine neurotransmission	Brain fog, low mood, anxiety, irritability	[8,10]
Essential for neurogenesis, myelination, and synaptic plasticity	Impaired neuroplasticity, decreased cognitive function	Difficulty with concentration, working and episodic memory	[8,9]
Stabilization of muscle function and oxygen transport	Decreased VO_2max, muscle insufficiency	Easy fatigue, feeling of lack of strength	[11,14]
Influence on cell proliferation and skin and hair function	Impaired tissue regeneration	Hair loss, pallor, dry skin	[12,13]

2.3 Diagnostic criteria for ferritin deficiency - controversy and interpretation of results

In clinical practice, a ferritin concentration of less than 30 ng/ml is commonly regarded as the lower limit of normal indicating reduced iron reserves, even with preserved haemoglobin levels. This value is used as a sensitive indicator of subclinical iron deficiency, especially in patients reporting non-specific symptoms such as chronic fatigue or weakness [15]. However, it should be remembered that ferritin, in addition to its iron storage function, also acts as an acute-phase protein, meaning that its concentration may be artificially inflated in the course of infection, inflammatory and chronic diseases, thereby masking systemic deficiencies. In such situations, it is increasingly suggested to use higher diagnostic thresholds, even up to 100 ng/ml, and the simultaneous determination of transferrin saturation (TSAT), whose value of less than 20% is a more stable indicator of available iron deficiency, less susceptible to the influence of inflammatory processes. Interpretation of the results should be particularly cautious in the case of co-occurring conditions that may disrupt ferritin levels independently of actual iron stores. This includes chronic liver disease, renal failure, obesity, pregnancy and alcoholism. In these contexts, the observed increase in ferritin does not necessarily correspond to the state of actual body stores. In contrast, in older people, vegetarians or vegans, physiologically lower ferritin values may not be of immediate clinical significance unless accompanied by symptoms or other laboratory abnormalities [16].

Therefore, the interpretation of ferritin should always be done in relation to the patient's clinical status, medical history and other iron management parameters. This approach allows the proper identification of latent iron deficiency, which, despite the absence of anaemia, can significantly affect the patient's functioning and remain unrecognised by routine laboratory assessment.

3. Relationship between low ferritin levels and iron supplementation and symptoms of chronic fatigue

Fatigue, understood as a subjective feeling of exhaustion and lack of energy, may be the body's defence mechanism against overuse of functional reserves and is a common symptom of many chronic diseases. Unlike acute, transient fatigue, chronic fatigue persists for more than six months, does not subside after rest and is not necessarily associated with physical exertion. A growing body of research indicates that one potential factor contributing to the development of this condition may be iron deficiency, even in the absence of anaemia [4].

One important piece of evidence supporting this relationship is a randomised trial that analysed the effect of iron supplementation on fatigue symptoms in premenopausal women without anaemia but with ferritin ≤ 50 ng/ml. Intravenous iron supply was shown to significantly reduce the severity of fatigue, and the greatest improvement was seen in participants with ferritin ≤ 15 ng/ml. More than 80% of them reported a subjective improvement in well-being after 6 and 12 weeks of therapy. Importantly, these improvements were not associated with an increase in haemoglobin levels, suggesting a red cell system-independent, metabolic effect of iron. Indeed, this element plays a key role in the function of mitochondrial enzymes, which are necessary for proper energy production. The results of the study support the concept that iron deficiency without anaemia may be an independent cause of fatigue, and that a ferritin concentration ≤ 15 ng/ml may be a practical indicator to consider implementing supplementation [17].

Similar conclusions have emerged from studies of mitochondrial mechanisms to explain the role of iron in the pathophysiology of fatigue. They have shown that this element is an integral component of the cytochromes that enable efficient cellular respiration. Deficiency of this element, even with normal haemoglobin levels, can lead to mitochondrial dysfunction, particularly by reducing the activity of complex I of the respiratory chain, which limits energy production in aerobic muscle [18].

Studies have shown that iron deficiency reduces the maximum oxygen consumption by tissues, leading to a compensatory increase in the load on the cardiovascular system and an intensification of fatigue symptoms. Importantly, even without an improvement in haematological parameters, iron supplementation resulted in an increase in VO_2max and improved exercise tolerance, suggesting that fatigue in the context of iron deficiency has an important metabolic and mitochondrial basis [14].

A French study that assessed the effect of iron deficiency on fatigue in menstruating women without anaemia also found consistent results. Female participants with ferritin levels below 50 µg/l complained of significant fatigue, although other clinical causes, including endocrine, psychiatric, cardiovascular, pulmonary or rheumatological disorders, were excluded. Iron supplementation for 12 weeks resulted in significant improvement, with fatigue severity reduced by almost 50% compared to baseline. Importantly, an increase in ferritin levels and improvements in blood morphological parameters such as haematocrit, mean erythrocyte volume (MCV) and transferrin levels were observed after just six weeks.

These results further confirm the efficacy of both oral and intravenous iron supplementation in alleviating fatigue symptoms and highlight the importance of ferritin as a clinical marker in qualifying for iron treatment, once other possible causes of chronic fatigue have been excluded [19].

It is also worth noting that iron deficiency can affect not only physical performance, but also the functioning of the central nervous system. Decreased serum ferritin levels may reflect impaired iron availability to neural tissues. Studies have shown that lower ferritin levels, as well as reduced red blood cell parameters (such as MCH and MCV), correlate with poorer performance on working memory tests and more errors in executive tasks. This suggests that iron deficiency may contribute to cognitive impairment through reduced information processing efficiency and impaired neurotransmission [20].

In addition, literature reviews indicate that iron deficiency may interfere with synaptic transmission and reduce neuronal plasticity, potentially explaining frequently observed neuropsychiatric symptoms such as cognitive decline, mood disorders (including depression) or reduced adaptive capacity of the nervous system. Thus, iron availability, as assessed by, among others, RBC parameters and ferritin levels, may be important not only in the context of physical fatigue, but also for the maintenance of normal mental and neurocognitive functioning, which are often an integral part of the clinical picture of chronic fatigue syndrome [8].

In conclusion, the results of numerous studies indicate that low ferritin levels, even with normal haemoglobin, may be an important pathophysiological factor in chronic fatigue syndrome. Iron deficiency affects not only energy metabolism and mitochondrial function, but also cognitive processes and neurotransmission, which may explain both the physical and neuropsychiatric symptoms observed in patients. Iron supplementation, especially in patients with ferritin ≤ 15 ng/ml, can provide significant improvement in symptoms of fatigue, even in the absence of anaemia. In clinical practice, the GP should consider determining ferritin levels in patients reporting chronic fatigue, especially after excluding other possible somatic and psychological causes.

4. Ferritin and chronic fatigue in post-COVID syndrome

Post-COVID-19 syndrome (so-called long COVID) develops in approximately 10-25% of recovered patients and includes a broad spectrum of persistent symptoms, irrespective of the severity of the acute infection. One of the most common and clinically debilitating symptoms is chronic fatigue, reported by up to 90% of patients. In some of these patients, the clinical picture meets the diagnostic criteria for chronic fatigue syndrome, suggesting a convergence of pathophysiological mechanisms. In this context, ferritin, an acute phase protein and the body's main iron store, is increasingly being analysed as a potential biomarker of this form of long COVID. Studies have shown that serum ferritin levels positively correlate with fatigue severity, depressive symptoms and overall severity of clinical presentation in patients with ME/CFS developing post-COVID-19. Although ferritin has traditionally been associated with iron deficiency and fatigue in the setting of hypoferritinaemia, hyperferritinaemia has been observed in post-COVID syndrome, particularly in women, which may indicate a different pathophysiological mechanism. Importantly, the elevated ferritin levels in these patients did not co-occur with other classical markers of inflammation, which may indicate its independent involvement in the disease process [21,22].

In addition to its iron storage function, ferritin can act as a pro-inflammatory molecule, activating cytokine pathways, including through NF-κB. Iron released from ferritin may catalyse radical reactions leading to oxidative stress and DNA damage, which may further impair mitochondrial and central nervous system function - elements that play a key role in the pathogenesis of ME/CFS. A possible influence of ferritin on endocrine function is also indicated. Studies have shown a negative correlation between its level and IGF-I concentration, which may indicate endocrine axis disruption, exacerbated by SARS-CoV-2 infection and its metabolic consequences [23].

In a study conducted at a Swiss tertiary neurological centre, chronic fatigue was the most common symptom in patients with post-COVID-19 syndrome, observed in more than 90% of the subjects, regardless of the severity of the acute infection. Ferritin levels remained elevated many months after the active phase of COVID-19 had expired, which was associated with increased production of cytokines, especially IL-6. The study's authors identified ferritin as a potential marker of not only diagnostic, but also therapeutic importance that could help identify patients requiring a more individualised approach [24].

Hyperferritinaemia in post-COVID syndrome may also result from chronic immune dysregulation, iron dyshomeostasis, and neuroendocrine disorders. These mechanisms include chronic CD8+ lymphocyte activation and abnormal NK cell function, as in non-COVID-19 ME/CFS. Hepcidin-like mechanisms induced by SARS-CoV-2 have also been proposed to be involved, which may affect ferritin accumulation independently of the acute inflammatory response. Furthermore, observations suggest an association of ferritin with psychiatric and endocrine disorders, such as depression, sleep disorders, hypertension or latent hypothyroidism [23].

Based on the available data, ferritin may act as an available and widely used biomarker to identify a subgroup of patients with long COVID at risk of developing ME/CFS, especially among women. Its role in pro-inflammatory, oxidative and endocrine processes indicates its potential usefulness not only in diagnosis, but also in monitoring the course and response to treatment. However, further research, both clinical and molecular, is needed to fully elucidate the importance of ferritin in the pathogenesis of chronic fatigue after COVID-19 and to realise its potential as an adjunct to personalised therapy.

5. Diagnostic and therapeutic problems

5.1 Difficulties in diagnosing chronic fatigue syndrome (CFS)

Significant difficulties are observed in the diagnosis of chronic fatigue syndrome due to the lack of unambiguous biomarkers and standardised diagnostic tools. Diagnostic criteria, such as the CDC, ME-ICC, Oxford or Canadian criteria, show significant differences in the range of symptoms required and the degree of restrictiveness, making it difficult to compare test results and complicating the clinical diagnostic process. The research highlights that none of the current methods have been sufficiently validated against diagnostic uncertainty, confirming the growing need to develop more reliable tools. The lack of biomarkers, especially one with known sensitivity and specificity, means that ME/CFS remains essentially a diagnosis of exclusion which prolongs patients' journey to an accurate diagnosis.

In addition, the symptoms of ME/CFS i.e. mainly chronic fatigue, post-exertional malaise, cognitive impairment and dysautonomia, co-occur with many other disease entities such as depression, fibromyalgia, hypothyroidism or underlying inflammation, increasing the risk of misclassification [5]. Although self-monitoring tools for symptoms (e.g. self-report scales) show some differential value, their validation on broad, clinically unclear populations is still limited. Another problem is the low clinical awareness among general practitioners, only about 23 % of general practitioners recognise ME/CFS as a distinct disease entity and only 17 %-14 % declare confidence in diagnosis and treatment. The low level of clinical knowledge and the persistent disbelief towards the somatic nature of ME/CFS contribute to the frequent downplaying of symptoms and their erroneous attribution to a psychosomatic aetiology. Lack of appropriate medical education results in delayed diagnosis and undermined patient credibility, which translates into a negative therapeutic experience and reduced quality of life for patients [25].

5.2. The role of ferritin in assessing the condition of the body – interpretative pitfalls

Ferritin is widely used in the diagnosis of iron deficiency, and its measurement in serum is commonly regarded as a reliable indicator of the body's iron stores. However, there are a number of limitations associated with its interpretation, particularly in the context of chronic fatigue or subclinical inflammation. Ferritin reference values are still a matter of debate. Adopting a lower limit of <15 µg/L, in line with the WHO definition (WHO, 2020), may fail to detect latent iron deficiency in patients with clinical symptoms, especially women, physically active individuals, and patients with ME/CFS. In athletes and patients with chronic fatigue, ferritin at the lower limit of normal (30–50 µg/L) is sometimes associated with impaired performance and concentration, despite formal laboratory normal and normal hemoglobin values [14].

Another interpretative difficulty is the fact that ferritin is an acute phase protein and its level increases in response to immune system activation. In chronic diseases such as ME/CFS, rheumatoid arthritis, or viral infections (including COVID-19), ferritin levels may be elevated regardless of actual iron status, leading to the erroneous conclusion that iron is sufficiently available [22,23,26].

This phenomenon, known as functional iron deficiency, requires additional complementary tests: TSAT, soluble transferrin receptor (sTfR) levels, and hepcidin to distinguish inflammation from actual deficiency [27].

Table 2. Laboratory and Clinical Criteria Differentiating Iron Deficiency Anemia and Latent Iron Deficiency. Own elaboration based on the literature.

	Iron Deficiency Anemia (IDA)	Latent Iron Deficiency (LID)	Source
Hemoglobin (Hb)	↓ (<12 g/dl in women, <13 g/dl in men)	Normal	[1]
Ferritin	↓ (<15 ng/ml)	↓ or borderline (15–30 ng/ml)	[17]
MCV (Mean Corpuscular Volume)	↓ (<80 fl)	Usually normal	[14]
MCH (Mean Corpuscular Hemoglobin)	↓	Normal or slightly ↓	[8]
Transferrin	↑	↑	[9]
Transferrin Saturation	↓ (<16%)	May be decreased or normal	[13]
CRP / ESR	Sometimes elevated in inflammation	Normal	[24]
Clinical Symptoms	Fatigue, pallor, shortness of breath, brittle nails, hair loss	Fatigue, reduced performance, brain fog	[14]
Response to Iron	Improvement in Hb and symptoms	Improvement in symptoms without change in Hb	[19,24]

In summary, ferritin is a useful but potentially misleading indicator. Its interpretation requires consideration of the broader clinical context, including the presence of inflammation, symptomatic presentation, and results of complementary tests. Otherwise, there is a risk of overlooking significant metabolic disorders that may contribute to chronic fatigue.

5.3. The need for an interdisciplinary approach

The diagnosis and treatment of chronic fatigue in the context of iron metabolism disorders requires the cooperation of specialists from various fields - internists, hematologists, sports nutritionists, trainers, and psychologists. An interdisciplinary approach allows for a comprehensive assessment of the patient, taking into account both biochemical parameters (ferritin, TSAT, hepcidin, sTfR) and dietary factors, lifestyle, level of physical activity, and mental state) [28,29]. Medical literature emphasizes that in the ME/CFS population, the effectiveness of therapy can be increased by integrating psychological support and lifestyle modifications, e.g., in the areas of regeneration and stress management, which affects not only the subjective feeling of fatigue, but also the effectiveness of iron supplementation and inflammatory processes [30]. In addition, complex cases, e.g., patients with gastrointestinal inflammation, require consultation with a gastroenterologist and sometimes diagnosis of underlying malabsorption disorders [31].

Such cooperation between specialists not only enables effective correction of iron metabolism disorders, but also identification and elimination of potential primary causes (e.g., subclinical inflammation), which plays a key role in the symptomatic treatment of chronic fatigue. Therefore, a multidisciplinary approach is the foundation of comprehensive care for patients with iron deficiency and chronic fatigue - it allows for precise diagnosis, optimization of therapy, and monitoring of effects, which increases the chances of improving performance, regeneration, and quality of life.

Disclosure

Author's contribution:
Conceptualization: WK, PSK, KJ, MG
Methodology: PSK, KJ, MG
Software: WK, PSK, KJ
Check: WK, PSK, MG
Formal analysis: PSK, KJ
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Resources: WK, PSK, KJ, MG
Data curation: KJ, MG
Writing - rough preparation: WK, PSK, KJ, MG
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