Pediatr Pol 2023; 98 (1): 57-65
DOI: https://doi.org/10.5114/polp.2023.126113
Submitted: 15.10.2022, Accepted: 25.11.2022, Published: 24.03.2023

PEDIATRIA Polska
Polish Journal of PAEDIATRICS

REVIEW PAPER

Ferritin – novel uses of a well-known marker in paediatrics

Aleksandra Izabella Rytel, Sandra Ostrowska, Katarzyna Marcinkiewicz, Maryna Krawczuk-Rybak, Małgorzata Sawicka-Żukowska

Department of Pediatric Oncology and Hematology, Medical University of Bialystok, Bialystok, Poland

ABSTRACT

Serum ferritin is one of the most widely used laboratory tests and is associated with both iron deficiency and iron overload. Currently, more and more attention is paid to the involvement of ferritin in processes other than iron metabolism. Low serum ferritin is unanimously associated with iron deficiency, while elevated serum ferritin may be a consequence of various medical conditions such as iron overload, an inflammatory process, SARS-CoV-2, organ failure, cancer, and endocrine disorders, including metabolic syndrome. We present a review of the literature on the role of ferritin in a variety of less obvious disease states in children.

KEY WORDS:

ferritin, iron metabolism, paediatrics, children.

INTRODUCTION

Ferritin is the longest studied protein involved in the metabolism of body iron. Ferritin was first described by the German pharmacologist Oswald Schmiederberg, who found the presence of an iron-rich component in horse liver [1]. For over 70 years ferritin has been analysed for its many functions, including its role in iron metabolism, cell proliferation, angiogenesis, inflammation, carcinogenesis, and immunosuppression [1–4]. Although its intracellular functions have been thoroughly described, the function of plasma ferritin is not fully understood. This protein is essential for iron storage and protecting cells from its harmful effects. Ferritin is composed of 24 subunit complexes, formed in a nanocage with iron trapped inside. Different subunits of ferritin – cytosol types – H, L, and mitochondrial type M are involved in different processes. The H and L subunits are responsible for varied functions and are present in different cell types [2, 4–6]. This explains the involvement of ferritin as a marker in various medical conditions. Plasma ferritin levels increase in acute and chronic inflammation, and this increase in serum correlates with the concentration of acute phase indicators such as C-reactive protein (CRP) [5–8].

Serum ferritin is widely used in both ambulatory and hospital diagnostics, usually to detect iron deficiency or overload [2–5]. It is a sensitive parameter, although its usefulness has some limitations especially related to its variability depending on different clinical states. Ferritin is often considered as low specificity because it can be elevated in a variety of inflammatory states, including cytokine release syndrome.

In this overview we present the non-obvious uses of ferritin in assessing the course and prognosis of various diseases in children.

FERRITIN IN CHILDHOOD INFECTIOUS DISEASES

SEPSIS

Biochemical markers such as ferritin have been used in studies to predict mortality in sepsis. Septic shock,

ADDRESS FOR CORRESPONDENCE:

Małgorzata Sawicka-Żukowska, Department of Pediatric Oncology and Hematology, Medical University of Bialystok, Bialystok, Poland, e-mail: mzukowska@interia.pl

the most severe complication of sepsis, together with macrophage activation syndrome (MAS), adult-onset Still's disease, and catastrophic antiphospholipid syndrome (cAPS) belong to Shoenfeld's syndrome (hyperferritinaemic syndrome) disease group, which share common clinical, laboratory, and therapeutic aspects and are characterized by hiperferritinaemia (ferritin > 400 μg/l) [9]. Since 2007, ferritin levels have been known to rise in children with septic shock, and its blood concentration > 500 μg/l has been associated with 3-fold higher mortality [10]. Increased ferritin levels in sepsis are associated with its function as an acute phase reactant, which occurs simultaneously with an inflammatory response mediated by cytokines such as TNFα, IFNγ, interleukin-1 (IL-1), interleukin-6 (IL-6), and elevated soluble CD163 (sCD163) – marker of activated macrophages [11]. Tonial *et al*. observed that ferritin ≥ 300 μg/l correlates with longer duration of total hospitalization and, in the intensive care unit, longer time of mechanical ventilation, higher need of vasopressor-inotropic support, and Paediatric Index of Mortality 2 (PIM2) [12]. Ferritin ≥ 1.980 μg/l combined with CRP ≥ 6.7 mg/ml indicates a 46% risk of death in PICU, whereas ferritin < 1.980 μg/l with the same CRP level provides only 4.65% risk of mortality [13].

Patients with ferritin levels ≥ 1000 μg/l had a considerably higher risk of DNAemia. Multiple DNA viruses were found in 93% of ferritin ≥ 1000 μg/l individuals, substantially related to the presence of Epstein-Barr virus, human herpesvirus 6, and adenovirus. Ferritin level also correlated with mortality, with the highest risk (56%) with concentrations ≥ 3000 μg/l [14].

Ferritin has the potential to be used in confirmation of early-onset sepsis in preterm newborns, which is a leading cause of morbidity and mortality. C-reactive protein, serum amyloid A, *Helicobacter pylori*, serum amyloid P, and ferritin (> 51 μg/l) were significantly raised in umbilical blood in a group with confirmed EOS in a study by Mithal *et al*., but more research is needed to confirm these relationships and the utility of probable markers [15].

COVID-19

The hyperinflammatory cytokine storm caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causes significantly more morbidity and mortality than any direct viral cytotoxicity. Some of the patients had a lower respiratory tract involvement – 61% of them had normal ferritin values based on age and sex reference values, while 39% had ferritin levels that were greater than reference values [16]. COVID-19 is a new member in the spectrum of hyperferritinaemic syndrome (besides adult-onset Still's disease, macrophage activation syndrome, cAPS, and septic shock).

The precise role of ferritin in the pathogenesis of COVID-19 at the cellular level has not yet been thoroughly determined. However, it is currently understood that cytokines increase the liver's production of defence proteins, such as ferritin and CRP, in response to injury. Primarily, IL-1β, IL-6, and IFN-γ molecules stimulate ferritin transcription and translation.

Macrophages and injured cells make up another possible cause for increased ferritin levels. Ferritin is significant because it encourages the release of additional pro-inflammatory mediators, which raises the inflammatory burden and creates a vicious cycle. Ferritin achieves this by activating NF-κB and increasing ferritin gene transcription [9].

Zachariah *et al*. analysed ferritin concentration and CRP in the severe phase of SARS-CoV-2 infection. In 53 of 58 patients a median ferritin concentration of 610 μg/l (IQR, 359–1280), and elevated CRP measured in 58 of 58 patients, were both consistent with severe inflammation. Those with severe illness exhibited higher peak levels of ferritin, together with IL-6 and D-dimer. High mean peak inflammatory markers were also seen in patients who needed mechanical breathing (ferritin, CRP, procalcitonin, D-dimer, and IL-6) [17–19].

Whittaker *et al*. noticed that children in the PIMS-TS (severe acute respiratory syndrome coronavirus 2) group (n = 13) who met the diagnostic criteria for Kawasaki disease (KD) were older, had higher ferritin, neutrophil, CRP, fibrinogen, and troponin levels and had lower lymphocyte counts than those with KD pre-COVID-19 [17].

Multisystem inflammatory syndrome in children was linked to elevated levels of blood biomarkers, including ferritin, CRP, D-dimer, and troponin, all of which indicate inflammation. High levels of these markers have also been linked to cytokine storm, multi-organ failure syndrome, and poor prognosis [20].

Children with critical COVID-19 had substantially higher levels of ferritin, IL-6, IL-10, and procalcitonin. It may be linked to the immunological dysregulation-induced systemic cytokine storm [21]. In terms of immunologic biomarkers, non-survivors had considerably higher levels of serum ferritin and IL-6 than survivors [19].

Findings imply that 7 indices (T, Th, Tc, IL-6, IL-10, RBC, and Hb) can assist clinicians diagnose COVID-19 severity in children early and provide a laboratory foundation for clinicians to treat children with serious COVID-19 [21]. It is recommended that serum ferritin, WBC count, lymphocyte count, platelet count, and IL-6 be monitored in hospitalized patients with respiratory distress as indicators for probable severe disease development [19].

Serum ferritin levels were high in 79% of children with cardiac involvement (median, 438 μg/l; IQR, 420–846 μg/l). All of these inflammatory indicators (ferritin, CRP, procalcitonin, and IL-6) were substantially higher ($p < 0.05$) in individuals who needed to be admitted to the intensive care unit compared to those who were handled just on the ward [22].

FERRITIN IN PSYCHIATRIC DISORDERS IN CHILDREN

ANOREXIA NERVOSA

The ferritin levels are higher in anorexic (AN) patients [23, 24]. The aetiology of this is uncertain. Starvation and life-threatening actions during AN causes laboratory changes [25]. Ferritin can be a biomarker of malnourishment rather than inflammation and may be used to guide the control of that condition. Kennedy *et al.* linked higher ferritin levels to iron storage following erythrocyte breakdown induced by low haematocrit levels caused by starvation [26]. Starvation occurring at the hepatocyte level can also activate ferritin synthesis [23].

Ferritin levels may be connected to high thyroid-stimulating hormone (TSH) in adolescents under the age of 16 years, which may help avoid the negative effects of iron deficiency and thyroid problems in AN patients [27]. Concerning dental issues, which are widespread in patients with eating disorders, Boillot *et al.* established that greater ferritin levels are connected with a higher likelihood of a generally decreased periodontium, particularly in women with AN ($p = 0.02$) [24]. Pettersson *et al.* showed that in 3 years' observation following hospitalization, ferritin levels were lower than at the beginning. The rationale was that more women had regular periods, which resulted in iron loss [28]. Moreover, when patients began to eat properly and gain weight, ferritin levels dropped significantly [23, 26].

FERRITIN IN ENDOCRINE DISEASES IN CHILDREN

OBESITY

In obese and overweight individuals, high ferritin was found to be an inflammatory indicator [9]. According to the findings of Shim *et al.*, ferritin is linked to insulin resistance (IR) and abdominal fat. In obese people ferritin correlates significantly with hyperglycaemia, triglycerides (TG), and IR indicators, as well as with whole-body fat ($p = 0.002$ for males but not females) [29]. In research by Shattnawi *et al.* obese adolescents had higher ferritin levels [30]. Furthermore, high ferritin levels were correlate with higher total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and TG in boys. However, in both girls and boys elevated ferritin was negatively linked to low high-density lipoprotein cholesterol (HDL-C) [31].

In the research conducted by Zhang *et al.* the optimum cut-off value for ferritin in nonalcoholic fatty liver disease (NAFLD) in obese individuals was ≥ 58.55 µg/l, with a sensitivity of 60.0% and a specificity of 77.9%. It was discovered that high ferritin levels were substantially related with the risk of NAFLD [32]. Ferritin in NAFLD can indicate pro-inflammatory cytokine activation, which can affect the liver [11, 33].

In adults, elevated ferritin correlates with hypertension and can influence atherosclerosis [34]. In a study by Alam *et al.* of obese grown-ups, elevated ferritin levels were connected to fat cell acute phase reactant production. A positive correlation between ferritin and increasing BMI (body mass index) was found [35].

In conclusion, the elevated ferritin levels in both adults and children are associated with metabolic syndrome, IR and abdominal fat [29], dyslipidaemia [31], diabetes [36], NAFLD [32], and hypertension [34].

METABOLIC SYNDROME

High ferritin levels can relate to excessive iron storage and oxidative damage as well as chronic inflammation, all of which can cause metabolic syndrome (MetS) components to develop [29, 37]. As discovered by Shim *et al.*, high ferritin levels correlate significantly with MetS elements: hyperglycaemia, TG, waist circumference, IR indicators, and whole-body fat [29].

Moreover, Suárez-Ortegón *et al.* found a significant correlation between ferritin and cardiometabolic risk factors in boys between the ages of 5 and 16 years, who experienced 2 or more episodes of increased ferritin concentration, particularly at the age of 5 years and throughout adolescence ($p < 0.05$) [38]. Elevated ferritin levels are also associated with MetS and increased alanine aminotransferase, which can suggest hepatocytes dysfunction as a cause of higher serum ferritin in blood [39].

What is more, Kim *et al.* in a cohort of 2414 teenagers [31], Ellidag *et al.* in a cohort of 4205 individuals [40], and Shim *et al.* in a study with 15,963 people [29] all observed the same negative connection between serum ferritin and HDL-C levels. However, according to Yi *et al.*, elevated ferritin raises HDL-C levels [39].

DIABETES MELLITUS

Patients with diabetes mellitus type 1 (T1DM) have higher ferritin levels ($p < 0.001$) than healthy individuals [36, 41]. Ferritin causes excessive capillary permeability in the inflammatory pathway, glomerular basement membrane thickening, and apoptosis of the endothelial cells [36].

A study by Metwalley *et al.* comparing ferritin levels in children with type 1 diabetes to healthy controls showed that ferritin levels were considerably higher ($p < 0.001$). In a diabetic group after controlling for age, gender, illness duration, BMI, blood pressure, HbA_{1c}, urine albumin excretion, and fasting lipids, ferritin was found to be an independent predictor of microvascular complications frequently observed in diabetic individuals ($p < 0.001$) [36]. What is more, a cut-off value of ferritin was found in patients with microvascular complica-

tions (163.6 μg/l, with sensitivity of 92.1% and specificity of 93.4%) [36].

Research done by Ayça *et al.* found no link between T1DM and various anaemia markers including haemoglobin, red cell distribution, serum iron, and total serum iron-binding capacity [41]. This finding implies that T1DM children were not at risk for anaemia. In addition, only ferritin was significantly elevated ($p = 0.001$) in T1DM patients, suggesting an inflammatory background in this group [41]. Furthermore, it was observed that elevated ferritin, when used as a risk factor for developing T1DM in childhood, is not an accurate predictor [42].

FERRITIN IN RHEUMATOLOGICAL DISEASES IN CHILDREN

In rheumatological diseases high ferritin levels are mainly associated with its aetiopathology. High serum ferritin levels are especially connected with systemic inflammatory response caused by co-existing MAS [43–47]. Macrophage activation syndrome, as a hyperferritinaemia and inflammatory cytokine indicator, is a common consequence of autoimmune disorders such as juvenile idiopathic arthritis (sJIA) [9, 11]. In rheumatic illnesses ferritin cut-off levels higher than 684 μg/l are thought to coexist with MAS [9].

KAWASAKI DISEASE

Although elevated ferritin is uncommon in KD, Kim *et al.* found a considerably higher ferritin level with a cut-off value of 120.8 μg/l, with sensitivity and specificity of 74.5% and 83.3%, respectively, when compared to other acute febrile diseases ($p = 0.003$) [43]. High ferritin levels in KD patients gradually decrease following IVIG therapy [43]. Consequently, individuals with IVIG resistance have higher ferritin levels [44, 48, 49].

In Kawasaki illness accompanied by MAS ferritin levels are closely associated [43–45]. In research by Kim *et al.* ferritin levels were substantially increased ($p = 0.001$) above 500 μg/l at the time of admission. Hyperferritinaemia in these patients was also linked to enlarged liver and spleen [31].

JUVENILE IDIOPATHIC ARTHRITIS

Serum ferritin concentrations are higher in sJIA than in KD patients [44]. According to Mizuta *et al.*, ferritin values were as follows: 1189 μg/l vs. median 146.5 μg/l, range: 14–2376 μg/l ($p < 0.0001$) in sJIA and KD, respectively. The serum ferritin threshold value was 369.6 μg/l [44]. Furthermore, sJIA, like KD, has greater ferritin levels when linked to MAS [46, 47]. In research by Guo *et al.* the median ferritin level was 1500.0 μg/l for patients with systemic JIA with MAS and 1246.0 μg/l for individuals with sJIA without MAS ($p < 0.01$) [46].

FERRITIN IN LUNG DISEASES IN CHILDREN

MYCOPLASMA PNEUMONIAE

In the early stage of *Mycoplasma pneumoniae* (MP) infection macrophages are activated to produce cytokines such as tumour necrosis factor TNF-α, which then induce ferritin synthesis. Higher ferritin levels suppress the immune system by inhibiting lymphocyte proliferation, which is also reflected in increased apoptosis by TNF-α [50].

Ferritin together with IL-18 and serum lactate dehydrogenase were studied to distinguish refractory and common pneumonias caused by MP. The results revealed that this combination was efficient in diagnosing the refractory type (persisting fever, worsening radiological findings, and ineffectiveness of macrolides) [50]. Ferritin was significantly higher among patients with only MP infection, treated by macrolides and methylprednisolone, in contrast to others ($p < 0.005$), which confirms previous studies [50, 51].

FERRITIN IN NEUROLOGICAL DISEASES IN CHILDREN

RESTLESS LEGS SYNDROME

Restless legs syndrome (RLS) is a neurological sleep disorder defined by an urge to move, and it is generally accompanied by unpleasant feelings as well as symptoms that are worse at rest, eased by movement, and most severe at night [52]. Dopaminergic dysregulation and brain iron abnormalities are linked to systemic iron shortage, circadian change in availability, or metabolic insufficiency in the substantia nigra [53]. Correlation between the incidence of RLS and iron deficiency anaemia was found in 61.2% of anaemic patients. Ferritin levels below 50 μg/l lead to the increasing frequency of RLS in both adults and children [54]. However, iron supplementation, despite a significant change in ferritin levels after 8 weeks of treatment, does not substantially reduce symptoms of RLS. At between 24 and 60 doses of iron the rise of ferritin did not correlate with the actual number of doses given. The supposed explanation is an increase in hepcidin, an iron homeostasis regulator, which, through a feedback loop mechanism, inhibits iron absorption in the intestine [55].

Periodic limb movement disorder (PLMD) is a similar condition, but it differs by occurring while sleeping in contrast to RLS, which occurs while awake [56]. Ferritin levels for PLMD patients were likewise below 50 μg/l in 71.8% of cases in the research by Simakajornboon *et al.* This group had a higher periodic limb movement index (PLMI) than those with ferritin higher than 50 μg/l. After 3 months of therapy with iron sulphate, the PLMI decreased signifi-

cantly, coinciding with a rise in ferritin (41–74 μg/l; $p < 0.001$ for both) [57].

It is noteworthy that both RLS and PLMD can coexist with attention deficit hyperactivity disorder (ADHD). All 3 diagnoses are thought to be mediated by the brain's dopamine production system, which is iron-dependent; hence, its low level may exacerbate manifestations common for these diseases: hyperactivity, irritability, and motor restlessness [56].

CEREBRAL PALSY

Cerebral palsy (CP), the most prevalent physical disability in children, affecting 2–3 out of 1000 births, has multiple aetiologies of brain injury, and about 90% of them occur during the perinatal period. Studies on CP patients have revealed a significant reduction in serum ferritin levels when compared to healthy control groups, implying that malnutrition affects iron [58, 59].

Although the role of iron in human studies on brain development is inconsistent, experiments on laboratory animals confirm the role of iron in myelination, learning memory, and cognitive and socio-emotional functioning [60]. Tomoum *et al*. discovered also a negative relationship between ferritin and the 5 grades of gross motor function categorization, the fifth of which includes the inability to maintain antigravity posture [59].

Ferritin trend was not associated with decreased haemoglobin, suggesting a potential role of ferritin as a marker of pre-anaemic phase in CP patients. Because children with CP frequently require multi-stage orthopaedic surgery, it is crucial to assess haemoglobin and ferritin levels to estimate the risk of postoperative anaemia and initiate preventive measures. Mohan *et al*. showed that 89% of children with CP were found to have low ferritin levels preoperatively compared to 18.2% in the control group [58]. In summary, ferritin levels should be measured in children with CP due to its role as indicator of malnutrition and early predictor of anaemia, as well as to prevent worsening of neuromotor symptoms.

FERRITIN IN PSYCHIATRIC DISORDERS IN CHILDREN

Attention deficit hyperactivity disorder is one of the most common disorders in child and adolescent psychiatry, with a frequency of over 5%. Low iron level, as measured by ferritin, may indicate a higher risk of hyperactivity [61]. In a study by Mahmoud *et al*. the mean ferritin concentration for children with ADHD was 24.8 ±14.1μg/l (range 3–65 μg/l) vs. 32.6 ±18.7 μg/l (range 7–72 μg/l) in healthy controls ($p = 0.03$). The decreased level of ferritin affected both hyperactive and inattentive types of ADHD [62]. A low level of iron, especially in the brain, which plays a crucial role in the production of dopamine, reflected by a lower level of ferritin, may lead to more apparent ADHD symptoms [63]. Attention deficit hyperactivity disorder is associated with comorbidities such as conduct disorder and specific learning difficulties, where increased ferritin levels have been observed. However, a negative correlation between ferritin and the overall number of psychiatric diagnoses in children with ADHD was found ($r = -351$; $p = 0.0001$) [64]. Attention deficit hyperactivity disorder is more common in children with epilepsy than in the general paediatric population (8–77%), and ferritin levels significantly increase in this comorbidity compared to only ADHD-affected or healthy patients [65].

About 30% of children with autism spectrum disorder suffer from iron deficiency, which has a negative impact on brain development [66]. In research by Bener *et al*., ferritin levels in autistic children were significantly lower than in the healthy control group ($p < 0.001$) [67].

Tourette syndrome is characterized by motor and verbal tics, and its aetiology is thought to be mostly due to genetic defects [68]. Low iron levels, and therefore ferritin levels, are considered to play a pathogenic role in tics [69]. In a study by Gorman ferritin was significantly lower (mean value 55 μg/l; $p = 0.03$) compared to controls (mean value 72.2 μg/l) but remained within acceptable limits. However, the intensity of ticks seems to have no connection with the ferritin concentration. A positive association between low ferritin and the putamen, sensorimotor, midtemporal, and subgenual cortices volume measured in MRI was found, which might indicate that ticks have less inhibitory control [69].

Also, ferritin can be used as a predictive factor in a child's development. There are reports that higher ferritin levels correlate with Early Learning Composite of cognitive functions (fine motor, visual reception, receptive language, expressive language) in 1–3-year-old children. With a concentration of 17 μg/l, the maximum level of early laparoscopic cholecystectomy (ELC) was obtained. A 5-unit rise in serum ferritin causes a 4-unit increase in ELC below the ELC maximum, but increases above the ELC maximum are relatively low. These findings suggest that the recommended cut-off value for ferritin in young children should be 17–18 μg/l [70].

FERRITIN IN CHILDHOOD INFECTIOUS DISEASES

FEBRILE SEIZURES

Fever can exacerbate the detrimental consequences of low ferritin levels on the brain, making seizures more likely [71]. Otherwise, low blood ferritin levels may reduce the seizure threshold because iron is required for the functioning of several enzymes and neurotransmitters in the central nervous system [72–74]. Köksal *et al*. showed that low serum ferritin levels [74] and iron deficiency may be risk factors for the onset of febrile seizures [72, 75].

According to Papageorgiou, iron deficiency, rather than anaemia, is linked to recurrence of seizures. Patients with a history of seizures had lower ferritin levels than individuals who had their first episode of seizures [76]. Similarly, the analysis of Daoud and Papageorgiou showed that plasma ferritin levels are considerably lower in children with complex febrile seizures [73, 76] whereas total iron binding capacity (TIBC) levels are much higher [76]. For children with a history or who are at high risk of febrile seizures, iron status screening should be considered as routine [76].

FERRITIN IN CARDIOVASCULAR DISEASES IN CHILDREN

The concentration of ferritin in children with various cardiovascular illnesses relies on iron status, inflammation, compensatory secondary erythrocytosis, and history of blood transfusions. Reduced iron in the myocardium is linked to a reduction in systolic function, which directly impacts heart function. Independent risk variables for right heart failure (HF) were higher pulmonary arterial systolic pressure and lower ferritin levels [77].

Patients with HF with isolated low ferritin levels that did not correspond to bone marrow iron insufficiency had a prognosis that was similar to those with normal ferritin values, so ferritin should not be used to detect iron shortage in HF patients, but it could be used as a safety criterion to avoid iron therapy in individuals with iron excess [78].

Due to compensatory secondary erythrocytosis, individuals with cyanotic congenital heart disease (CCHD) are predisposed to iron shortage. In the CCHD group, iron-deficient participants had substantially lower mean serum ferritin levels than those who were iron-sufficient (0.077 ±0.046 μg/l vs. 0.84 ±0.117 μg/l; $p < 0.001$). There were no significant changes in serum ferritin levels or mean TIBC between the CCHD and control groups among children aged 6–23 months [79].

Arrhythmias may be linked to iron deficiency in children who do not have structural cardiac disease. Pw, Pw max, and Pw dis; QT, QTc, and QTc dis; Tp-Te, Tp-Te dis, Tp-Te/QT, and Tp-Te/QTc were substantially longer in children with low ferritin levels (< 15 μg/l) compared to the group with ferritin > 25 μg/l ($p < 0.05$). There was no change in left ventricular diastolic end wall thicknesses (IVST, PWT) or left ventricle contractility indices (LVEF, LVSF) between the patients with low ferritin levels and the control group [80].

Due to iron overload and anaemia, multitransfused children are more prone to left ventricular diastolic dysfunction, which is indicated by poor relaxation. Left ventricular FS (fractional shortening) and serum ferritin level had a weak negative connection ($r = 0.77$, $p < 0.001$). Chelation therapy and high adherence to keep ferritin levels below 1000 μg/l result in a favourable cardiovascular prognosis [81].

TABLE 1. Trends in ferritin concentration in selected medical conditions

Trend in ferritin concentration	Medical condition
↑	Sepsis [10, 12–15] COVID-19 [17, 18] Anorexia [23–27] Obesity [29–32] Metabolic syndrome [38, 39] Diabetes mellitus [41, 42] Kawasaki disease [43] sJIA [44] *M. pneumoniae* [50, 51]
↓	RLS, PLMS [54–57] Cerebral palsy [58–60] ADHD [65] Autism [66, 67] Tourette syndrome [68, 69] Febrile seizures [71–75] Left ventricular fractional shortening [81] Tuberculosis [83–86]

ADHD – attention deficit hyperactivity disorder, PLMS – periodic limb movement in sleep, RLS – restless legs syndrome, sJIA – such as juvenile idiopathic arthritis

FERRITIN IN LUNG DISEASES IN CHILDREN

TUBERCULOSIS

Iron is an essential factor for the growth and virulence of *Mycobacterium tuberculosis*. To compete for the mentioned microelement with the host, this pathogen produces siderophores, which are extracellular binding molecules capable of removing iron from both transferrin and ferritin. Iron is transported from transferrin to ferritin and stored intracellularly as part of a physiological process in the human body. In defence mechanisms, the quantity of transferrin, as well as the uptake of dietary iron, is reduced during bacterial infection. Consequently ferritin levels are also affected and decrease [82].

Tuberculosis can have active form with symptoms or latent (LTBI) without clinical manifestation; however, mycobacterial antigens are detected in both cases [83]. In a study by Comella-Del-Barrio *et al.* ferritin differentiated QFT-GIT-positive patients in active and latent infection groups with high success ($p = 0.019$; mean value for active:109 μg/l; LTBI: 52.5 μg/l). Nevertheless, a combination of IP-10, IFN-gamma, ferritin, and 25(OH)D had the highest diagnostic performance to distinguish between active TB (93.2%) and LTBI (90%) [84]. In a study comparing the performance of these tests, in the TST-negative group, lower ferritin was associated with QFT (IGRA QuantiFERON-TB Gold In-Tube)-positive results ($p = 0.036$; cut-off for differentiating QFT+ and QFT = 37.5 μg/l). In the TST-QFR+ group, besides low ferritin level, the time of exposure was shorter (< 2 months). This suggests that

QFT is a faster test, and ferritin could be a marker for primary tuberculosis infection in its early stages [85].

It was observed that colony-stimulating factor ferritin levels were lower in patients with tuberculous meningitis (TBM)-related stroke (mean value 6.8634 μg/l) compared to children with TBM without stroke (mean value 11.5167 μg/l). The tendency was opposite for ferritin serum levels; it was higher in TBM-related stroke [86].

CONCLUSIONS

Ferritin levels differ significantly depending on the ailment for which they are measured, and this can be caused by a variety of factors. As shown, both increasing and decreasing ferritin concentrations are related to progression or stadium of the disease (Table 1). Ferritin levels might be used to predict the prognosis of some diseases, and they frequently correlate with other indicators, not just biochemical ones. As a result, ferritin appears to have a greater impact than previously thought.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Harrison PM, Arosio P. The ferritins: molecular properties, iron storage function and cellular regulation. Biochim Biophys Acta 1996; 1275: 161-203.
2. Alkhateeb AA, Connor JR. Nuclear ferritin: a new role for ferritin in cell biology. Biochim Biophys Acta 2010; 1800: 793-797.
3. Beaton MD, Adams PC. Treatment of hyperferritinemia. Ann Hepatol 2012; 11: 294-300.
4. Cullis JO, Fitzsimons EJ, Griffiths WJ, et al. Investigation and management of a raised serum ferritin. Br J Haematol 2018; 181: 331-340.
5. Alkhateeb AA, Connor JR. The significance of ferritin in cancer: anti-oxidation, inflammation and tumorigenesis. Biochim Biophys Acta 2013; 1836: 245-254.
6. Chiou B, Connor JR. Emerging and dynamic biomedical uses of ferritin. Pharmaceuticals (Basel) 2018; 11: 124.
7. Łęcka M, Słomka A, Albrecht K, et al. Unbalance in iron metabolism in childhood leukemia converges with treatment intensity: biochemical and clinical analysis. Cancers (Basel) 2021; 13: 3029.
8. Récher C. Clinical implications of inflammation in acute myeloid leukemia. Front Oncol 2021; 11: 623952.
9. Mahroum N, Alghory A, Kiyak Z, et al. Ferritin – from iron, through inflammation and autoimmunity, to COVID-19. J Autoimmun 2022; 126: 102778.
10. Garcia PC, Longhi F, Branco RG, et al. Ferritin levels in children with severe sepsis and septic shock. Acta Paediatr 2007; 96: 1829-1831.
11. Kernan KF, Carcillo JA. Hyperferritinemia and inflammation. Int Immunol 2017; 29: 401-409.
12. Tonial CT, Garcia PCR, Schweitzer LC, et al. Cardiac dysfunction and ferritin as early markers of severity in pediatric sepsis. J Pediatr (Rio J) 2017; 93: 301-307.
13. Carcillo JA, Sward K, Halstead ES, et al. A systemic inflammation mortality risk assessment contingency table for severe sepsis. Pediatr Crit Care Med 2017; 18: 143-150.
14. Simon DW, Halstead ES, Davila S, et al. DNA viremia is associated with hyperferritinemia in pediatric sepsis. J Pediatr 2019; 213: 82-87.e2.
15. Mithal LB, Palac HL, Yogev R, et al. Cord blood acute phase reactants predict early onset neonatal sepsis in preterm infants. PLoS One 2017; 12: e0168677.
16. Giannattasio A, D'Anna C, Muzzica S, et al. Is COVID-19 a hyperferritinemic syndrome in children? Clin Chem Lab Med 2021; 59: e409-e412.
17. Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA 2020; 324: 259-269.
18. Zachariah P, Johnson CL, Halabi KC, et al. Epidemiology, clinical features, and disease severity in patients with coronavirus disease 2019 (COVID-19) in a children's hospital in New York City, New York. JAMA Pediatr 2020; 174: e202430.
19. Henry BM, de Oliveira MHS, Benoit S, et al. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med 2020; 58: 1021-1028.
20. Pereira MFB, Litvinov N, Farhat SCL, et al. Severe clinical spectrum with high mortality in pediatric patients with COVID-19 and multisystem inflammatory syndrome. Clinics (Sao Paulo) 2020; 75: e2209.
21. Lu W, Yang L, Li X, et al. Early immune responses and prognostic factors in children with COVID-19: a single-center retrospective analysis. BMC Pediatr 2021; 21: 181.
22. Valverde I, Singh Y, Sanchez-de-Toledo J, et al. Acute cardiovascular manifestations in 286 children with multisystem inflammatory syndrome associated with COVID-19 infection in Europe. Circulation 2021; 143: 21-32.
23. Papillard-Marechal S, Sznajder M, Hurtado-Nedelec M, et al. Iron metabolism in patients with anorexia nervosa: elevated serum hepcidin concentrations in the absence of inflammation. Am J Clin Nutr 2012; 95: 548-554.
24. Boillot A, Ringuenet D, Kapila Y, et al. High serum ferritin levels are associated with a reduced periodontium in women with anorexia nervosa. Eat Weight Disord 2020; 25: 1763-1770.
25. Pires SAP, Soares JC, Luz AMBD, et al. Outpatient analytic assessment of anorexia nervosa – the importance of venous blood gases. Rev Paul Pediatr 2020; 38: e2018358.
26. Kennedy A, Kohn M, Lammi A, et al. Iron status and haematological changes in adolescent female inpatients with anorexia nervosa. J Paediatr Child Health 2004; 40: 430-432.
27. Salinas M, López-Garrigós M, Flores E, et al. Automated requests for thyroid-stimulating hormone and ferretin tests in young primary care patients with anorexia as an intervention to improve detection of underlying conditions. Lab Med 2019; 50: 268-272.
28. Pettersson C, Svedlund A, Wallengren O, et al. Dietary intake and nutritional status in adolescents and young adults with anorexia nervosa: a 3-year follow-up study. Clin Nutr 2021; 40: 5391-5398.
29. Shim YS, Kang MJ, Oh YJ, et al. Association of serum ferritin with insulin resistance, abdominal obesity, and metabolic syndrome in Korean adolescent and adults: The Korean National Health and Nutrition Examination Survey, 2008 to 2011. Medicine (Baltimore) 2017; 96: e6179.
30. Shattnawi KK, Alomari MA, Al-Sheyab N, et al. The relationship between plasma ferritin levels and body mass index among adolescents. Sci Rep 2018; 8: 15307.
31. Kim YE, Kim DH, Roh YK, et al. Relationship between serum ferritin levels and dyslipidemia in Korean adolescents. PLoS One 2016; 11: e0153167.

32. Zhang J, Cao J, Xu H, et al. Ferritin as a key risk factor for nonalcoholic fatty liver disease in children with obesity. J Clin Lab Anal 2021; 35: e23602.
33. Lombardi R, Pisano G, Fargion S. Role of serum uric acid and ferritin in the development and progression of NAFLD. Int J Mol Sci 2016; 17: 548.
34. Ryoo JH, Kim SY, Oh CM, et al. The incidental relationship between serum ferritin levels and hypertension. Int J Cardiol 2015; 183: 258-262.
35. Alam F, Memon AS, Fatima SS. Increased body mass index may lead to hyperferritinemia irrespective of body iron stores. Pak J Med Sci 2015; 31: 1521-1526.
36. Metwalley KA, Raafat DM, Tamer DM, et al. Ferritin levels in children and adolescents with type 1 diabetes mellitus: relationship with microvascular complications and glycemic control. Arch Endocrinol Metab 2021; 64: 720-725.
37. Hämäläinen P, Saltevo J, Kautiainen H, et al. Serum ferritin levels and the development of metabolic syndrome and its components: a 6.5-year follow-up study. Diabetol Metab Syndr 2014; 6: 114.
38. Suárez-Ortegón MF, Blanco E, McLachlan S, et al. Ferritin levels throughout childhood and metabolic syndrome in adolescent stage. Nutr Metab Cardiovasc Dis 2019; 29: 268-278.
39. Yi KH, Hwang JS, Lim SW, et al. Ferritin level is associated with metabolic syndrome and elevated alanine aminotransferase in children and adolescents. J Pediatr Endocrinol Metab 2016; 29: 1337-1344.
40. Ellidag HY, Eren E, Akdag M, et al. The relationship between serum ferritin levels and serum lipids and HDL function with respect to age and gender. Ukr Biochem J 2016; 88: 76-86.
41. Ayça S, Duru NS, Elevli M. Effects of anaemia parameters on metabolic control in children with type-1 diabetes mellitus. Istanbul Med J 2020; 21: 397-400.
42. Størdal K, McArdle HJ, Hayes H, et al. Prenatal iron exposure and childhood type 1 diabetes. Sci Rep 2018; 8: 9067.
43. Kim SH, Song ES, Yoon S, et al. Serum ferritin as a diagnostic biomarker for Kawasaki disease. Ann Lab Med 2021; 41: 318-322.
44. Mizuta M, Shimizu M, Inoue N, et al. Serum ferritin levels as a useful diagnostic marker for the distinction of systemic juvenile idiopathic arthritis and Kawasaki disease. Mod Rheumatol 2016; 26: 929-932.
45. Roh DE, Kwon JE, Choi HJ, et al. Importance of serum ferritin level for early diagnosis and differentiation in patients with Kawasaki disease with macrophage activation syndrome. Children (Basel) 2021; 8: 269.
46. Guo L, Xu Y, Qian X, et al. Sudden hypotension and increased serum interferon-γ and interleukin-10 predict early macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis. J Pediatr 2021; 235: 203-211.e3.
47. Fall N, Barnes M, Thornton S, et al. Gene expression profiling of peripheral blood from patients with untreated new-onset systemic juvenile idiopathic arthritis reveals molecular heterogeneity that may predict macrophage activation syndrome. Arthritis Rheum 2007; 56: 3793-3804.
48. Kong WX, Ma FY, Fu SL, et al. Biomarkers of intravenous immunoglobulin resistance and coronary artery lesions in Kawasaki disease. World J Pediatr 2019; 15: 168-175.
49. Yamamoto N, Sato K, Hoshina T, et al. Utility of ferritin as a predictor of the patients with Kawasaki disease refractory to intravenous immunoglobulin therapy. Mod Rheumatol 2015; 25: 898-902.
50. Choi YJ, Jeon JH, Oh JW. Critical combination of initial markers for predicting refractory Mycoplasma pneumoniae pneumonia in children: a case control study. Respir Res 2019; 20: 193.
51. Tamura A, Matsubara K, Tanaka T, et al. Methylprednisolone pulse therapy for refractory Mycoplasma pneumoniae pneumonia in children. J Infect 2008; 57: 223-228.
52. Allen RP, Picchietti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003; 4: 101-119.
53. Klingelhoefer L, Bhattacharya K, Reichmann H. Restless legs syndrome. Clin Med (Lond) 2016; 16: 379-382.
54. Halac G, Sezer GM, Saglam NO, et al. The relationship between Willis-Ekbom disease and serum ferritin levels among children in Northwestern Turkey. Neurosciences (Riyadh) 2015; 20: 336-340.
55. Rosen GM, Morrissette S, Larson A, et al. Does Improvement of low serum ferritin improve symptoms of restless legs syndrome in a cohort of pediatric patients? J Clin Sleep Med 2019; 15: 1149-1154.
56. Maheswaran M, Kushida CA. Restless legs syndrome in children. MedGenMed 2006; 8: 79.
57. Simakajornboon N, Gozal D, Vlasic V, et al. Periodic limb movements in sleep and iron status in children. Sleep 2003; 26: 735-738.
58. Mohan R, Unnikrishnan PN, George H, et al. Is ferritin estimation and optimisation important in cerebral palsy children undergoing single event multilevel surgery? J Orthop 2019; 16: 1-4.
59. Tomoum HY, Badawy NB, Hassan NE, et al. Anthropometry and body composition analysis in children with cerebral palsy. Clin Nutr 2010; 29: 477-481.
60. McCann S, Perapoch Amadó M, Moore SE. The role of iron in brain development: a systematic review. Nutrients 2020; 12: 2001.
61. Oner O, Oner P, Bozkurt OH, et al. Effects of zinc and ferritin levels on parent and teacher reported symptom scores in attention deficit hyperactivity disorder. Child Psychiatry Hum Dev 2010; 41: 441-447.
62. Mahmoud MM, El-Mazary AA, Maher RM, et al. Zinc, ferritin, magnesium and copper in a group of Egyptian children with attention deficit hyperactivity disorder. Ital J Pediatr 2011; 37: 60.
63. Juneja M, Jain R, Singh V, et al. Iron deficiency in Indian children with attention deficit hyperactivity disorder. Indian Pediatr 2010; 47: 955-958.
64. Öztürk Y, Topal Z, Demir N, et al. Iron and ferritin levels of children and adolescents with ADHD and ADHD-NOS. J Pediatr Res 2020; 7: 216-222.
65. Abd El Naby SA, Naguib YM. Sociodemographic, electrophysiological, and biochemical profiles in children with attention deficit hyperactivity disorder and/or epilepsy. Behav Neurol 2018; 2018: 8932817.
66. Chen MH, Su TP, Chen YS, et al. Association between psychiatric disorders and iron deficiency anemia among children and adolescents: a nationwide population-based study. BMC Psychiatry 2013; 13: 161.
67. Bener A, Khattab AO, Bhugra D, et al. Iron and vitamin D levels among autism spectrum disorders children. Ann Afr Med 2017; 16: 186-191.
68. Eapen V, Usherwood T. Tourette syndrome in children. Aust J Gen Pract 2021; 50: 120-125.
69. Gorman DA, Zhu H, Anderson GM, et al. Ferritin levels and their association with regional brain volumes in Tourette's syndrome. Am J Psychiatry 2006; 163: 1264-1272.
70. Parkin PC, Koroshegyi C, Mamak E, et al. Association between serum ferritin and cognitive function in early childhood. J Pediatr 2020; 217: 189-191.
71. Ahmed BW, Hanoudi BM, Ibrahim BA. Risk factors in children with febrile seizures and their iron status. J Pak Med Assoc 2019; 69: S22-S25.
72. Zareifar S, Hosseinzadeh HR, Cohan N. Association between iron status and febrile seizures in children. Seizure 2012; 21: 603-605.
73. Daoud AS, Batieha A, Abu-Ekteish F, et al. Iron status: a possible risk factor for the first febrile seizure. Epilepsia 2002; 43: 740-743.

74. Köksal AO, Özdemir O, Büyükkaragöz B, et al. The association between plasma ferritin level and simple febrile seizures in children. J Pediatr Hematol Oncol 2016; 38: 512-516.
75. Jang HN, Yoon HS, Lee EH. Prospective case control study of iron deficiency and the risk of febrile seizures in children in South Korea. BMC Pediatr 2019; 19: 309.
76. Papageorgiou V, Vargiami E, Kontopoulos E, et al. Association between iron deficiency and febrile seizures. Eur J Paediatr Neurol 2015; 19: 591-596.
77. Yu J, Yu L, Li Y, et al. Iron deficiency is a possible risk factor causing right heart failure in Tibetan children living in high altitude area. Medicine (Baltimore) 2020; 99: e21133.
78. Grote Beverborg N, Klip IT, Meijers WC, et al. Definition of iron deficiency based on the gold standard of bone marrow iron staining in heart failure patients. Circ Heart Fail 2018; 11: e004519.
79. Itiola AY, Animasahun BA, Njokanma OF. Serum iron status of children with cyanotic congenital heart disease in Lagos, Nigeria. Sultan Qaboos Univ Med J 2019; 19: e345-e351.
80. Demir F, Kayali S, Gokcebay DG. Does iron deficiency affect the heart in children? J Pediatr Hematol Oncol 2022; 44: 84-88.
81. El-Waseef MM, Taha S, Elgindi H. Left ventricular diastolic abnormalities and the impact of hepatitis C virus infection in multitransfused Egyptian children. Arch Med Sci 2010; 6: 96-99.
82. Ratledge C. Iron, mycobacteria and tuberculosis. Tuberculosis (Edinb) 2004; 84: 110-130.
83. Carvalho I, Goletti D, Manga S, et al. Managing latent tuberculosis infection and tuberculosis in children. Pulmonology 2018; 24: 106-114.
84. Comella-Del-Barrio P, Abellana R, Villar-Hernández R, et al. A model based on the combination of IFN-γ, IP-10, ferritin and 25-hydroxyvitamin D for discriminating latent from active tuberculosis in children. Front Microbiol 2019; 10: 1855.
85. Pérez-Porcuna TM, Ascaso C, Malheiro A, et al. Mycobacterium tuberculosis infection in young children: analyzing the performance of the diagnostic tests. PLoS One 2014; 9: e97992.
86. Manyelo CM, Chegou NN, Seddon JA, et al. Serum and cerebrospinal fluid host proteins indicate stroke in children with tuberculous meningitis. PLoS One 2021; 16: e0250944