Brief Reviews

Update in Hyperferritinemic Syndromes: Recognition and Management - A Scoping Review

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Journal of Brown Hospital Medicine
Vol. 1, Issue 3, 2022

Article Information

Keywords: hyperferritinemic, hemophagocytic lymphohistiocytosis, macrophage activation syndrome, catastrophic antiphospholipid syndrome, septic shock, adult-onset Still's Disease, multi- inflammatory syndrome

https://doi.org/10.56305/001c.37667

Submitted: July 12, 2022 EST

Accepted: August 15, 2022 EST

Abstract

Elevated serum ferritin is a marker of macrophage activation and is associated with increased mortality. The hyperferritinemic syndromes which include hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), catastrophic antiphospholipid syndrome (CAPS), septic shock, adult-onset Still's Disease (AOSD), and multi-inflammatory syndrome related to COVID-19 (MIS-C/A) are characterized by intense inflammation and its sequalae. Prompt recognition and management of these heterogenous disorders is required to improve patient outcomes. We perform a scoping review of the existing literature on the key features of these rare syndromes.

INTRODUCTION

Ferritin is an iron storage shell protein composed of 24 light (FTL) or heavy (FTH) ferritin monomers synthesized and stored in hepatocytes.[1] Even though FTL is the most common monomer, the FTL to FTH ratio differs depending on tissue and is dynamic.[2] Serum ferritin is a well-known acute-phase reactant. Its levels reflect macrophage immune response and the degree of acute and chronic inflammation. In general, serum ferritin has a high ratio of FTL to FTH.[2-4]

Ferritin participates in host immune responses. FTH increases in inflammatory settings and has many immunomodulatory properties.[5,6] Its immunomodulatory effects include induction of the anti-inflammatory cytokine interleukin-10 (IL-10), suppression of lymphopoiesis type IV hypersensitivity reaction, induction of T-cell anergy and a decrease in antibody production.[7-10]

Normal ferritin levels range between 12 and 300 ng/mL for men and between 12 and 150 ng/mL for women. High levels of serum ferritin have been reported in various acute or chronic inflammatory conditions including infectious, rheumatologic, hematologic, and malignant diseases. Hyperferritinemia in general is considered a marker of macrophage activation and is associated with high mortality.[11] During the hyperferritinemic state, reticuloendothelial system activation, combined with elevated cytokine levels can lead to multiple organ dysfunction via induction of inflammatory pathways.[12-14]

Hyperferritinemia, defined as serum ferritin above 500 ng/mL, can be seen in hemophagocytic lymphohistiocytosis (HLH) and its secondary subcategory, macrophage activation syndrome (MAS), catastrophic antiphospholipid syndrome (CAPS), septic shock, adult-onset Still's Disease (AOSD), and more recently multi-inflammatory syndrome related to COVID-19 (MIS-C/A).[15-17]

Diagnosis and management of hyperferritinemic syndromes may be challenging due to their rarity, which may delay diagnosis. Therapeutic options are often empiric. In this review we outline key aspects of these conditions to aid clinicians in both recognition and management.

METHODS

This scoping review was completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) checklist. We searched for English-language published studies in MEDLINE (up to July 31, 2022), discovered through multiple search queries specifying for "Macrophage activation syndrome" OR "MAS", "Hemophagocytic lymphohistiocytosis" OR "HLH", "Sepsis" OR "Shock" OR "Septic shock", "catastrophic antiphospholipid syndrome" OR "CAPS", "Still's Disease" OR "Adult Onset Still's Disease" OR "AOSD", "Multisystem inflammatory syndrome" OR "MIS-C" OR "MIS-A", and "Hyperferritinemia" OR "Hyperinflammatory syndrome" OR "Hyperinflamma-

tion" to capture remaining studies not discovered by searches specifying clinical conditions/syndromes.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) AND MACROPHAGE ACTIVATION SYNDROME (MAS)

HLH is a rare, life-threatening condition that is divided into primary and secondary subtypes. Genetic mutations which impair the function of natural killer (NK) and cytotoxic T cells cause primary HLH, a condition that typically presents in infancy and childhood.[18] Some mutations in gene loci that are associated with familial HLH can cause late-onset primary HLH in adults.[19] The most common causes of secondary HLH include infections, autoimmune diseases and malignancies.[20]

Regarding infections, certain viral, particularly Epstein–Barr virus (EBV), bacterial, fungal or parasitic infections can cause hyperferritinemia and secondary HLH.[21-28] Most commonly it is seen in children with the systemic form of juvenile idiopathic arthritis (sJIA), and its adult form, AOSD.[29-31] Other causes of MAS include systemic lupus erythematosus (SLE), Kawasaki disease, rheumatoid arthritis, and various rheumatologic diseases.[32-36] Malignancy-associated HLH is seen mainly in adults with hematologic malignancies such as T cell leukemias and lymphomas (0.9%-1.3%).[37,38] A higher rate has been reported in Japanese and Eastern Asian origin patients.[39]

Most of our understanding on the pathophysiology of HLH/MAS is derived from findings on primary HLH and familial subtypes. It is thought that NK cells and cytotoxic CD8 T cells become unable to lyse infected or otherwise activated antigen-presenting cells (APCs). Prolonged interactions between activated white blood cells thus lead to the amplification of the pro-inflammatory cytokine cascade. This loss-of-function of NK and cytotoxic T cells is further worsened under hypercytokinemic state.[18,40] TNF-α, IFN-γ, IL-1, IL-10, IL-12, IL-18, M-CSF and particularly IL-6 play a significant role.[12,13,41-45] Eventually, activated macrophages cause hemophagocytosis, resulting in multi-organ dysfunction.

There are limited epidemiological data on the incidence of HLH/MAS. The annual incidence of HLH in children and adults was determined to be 1 per 800,000 at a nationwide survey in Japan.[46] HLH diagnosis in pediatric patients is close to 1 case per 3000 admissions.[47]

As a result of immune dysregulation, HLH/MAS usually presents with a wide spectrum of clinical features.[48] Diagnostic criteria for HLH diagnosis in children were developed per the HLH-2004 protocol, and are shown in **Table 1**.[48] These criteria are also commonly used for HLH diagnosis in adults. Notably, some clinical manifestations that are regularly observed in adults are excluded from these criteria, such as elevated transaminases, especially AST (aspartate aminotransferase), elevated serum D-dimer and abnormal coagulation labs, elevated LDH (lactate dehydrogenase) and CRP (C-reactive protein) levels, hyponatremia, maculopapular rash, and neurologic abnormalities. Neurologic manifestations can be seen in one-third of patients including seizures, altered mental status, ataxia, and posterior reversible encephalopathy syndrome (PRES).[49-51]

Table 1. HLH-2004 diagnostic criteria

Diagnostic criteria (5 out of 8 required)
Cytopenias (affecting ≥2 of 3 lineages in peripheral blood) *
Fever ≥38.5°C
Hypertriglyceridemia and/or hypofibrinogenemia
Fasting triglycerides >265 mg/dL, fibrinogen <150 mg/dL
Ferritin >500 ng/mL
Splenomegaly
Low or absent NK cell activity
Elevated soluble CD25 sIL2R (>2,400 U/mL)
Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver

*hemoglobin <9 g/dL (for infants <4 weeks, hemoglobin <10 g/dL); platelets <100,000/microL; absolute neutrophil count <1000/microL

Results of sIL2r (soluble CD-25) levels and NK cell activity are not usually available expeditiously, and assays of heterozygous allele mutation do not always have specific or measurable clinical significance. In contrast to these shortcomings, the Hscore shown in **Table 2**, generates a probability for an HLH diagnosis without considering the sIL2r levels and NK cell activity. By setting a cutoff of 168, Hscore appears to have slightly superior diagnostic accuracy (100% sensitivity, 94.1% specificity) compared to the HLH-2004 diagnostic criteria in adults (95% sensitivity, 93.6% specificity).[52]

It is more challenging to diagnose MAS in rheumatologic diseases, as there is a high rate of overlap between clinical features of underlying disease and MAS. Especially, acute sJIA is difficult to differentiate from MAS.[53] In such cases, the newer 2016 classification criteria for MAS in sJIA (**Table 3**) is used for assisting in the diagnosis.

The role of ferritin levels in the diagnosis of primary or secondary HLH is crucial. In children with primary HLH, ferritin levels greater than 500, 5,000, and 10,000 ng/mL were seen in 93%, 42%, and 25% of patients, respectively.[54,55] Ferritin levels >3,000 ng/mL should raise high clinical suspicion of HLH/MAS.[47,56]

Treatment guidelines for HLH/MAS are mainly based on the HLH-94 protocol and its modified recommendations, the HLH-2004 protocol.[48,54,55,57] Generally, in cases of mild severity the first therapeutic step is high-dose glucocorticoids and treatment of the underlying condition.[48,55,57] This is particularly important for infectious causes since an early diagnosis of infection and empirical initiation of appropriate antimicrobial treat-

Table 2. Elements of the H Score

Known underlying immunosuppression	Yes/No
Temperature	<38.4°C 38.4-39.4°C ≥39.5°C
Organomegaly	None Hepatomegaly OR splenomegaly Hepatomegaly AND splenomegaly
Cytopenia	of 1 lineage of 2 lineages of 3 lineages
Ferritin	<2000 ng/mL 2000-6000 ng/mL >6000 ng/mL
Triglycerides	<1.5 mmol/L 1.5-4.0 mmol/L >4.0 mmol/L
Fibrinogen	>2.5 g/L ≤2.5 g/L
AST	<30 IU/L ≥30 IU/L

AST - aspartate aminotransferase

Table 3. 2016 Classification criteria for MAS in sJIA patients

Fever	
Ferritin	>684 ng/mL
2 of the following:	
Thrombocytopenia	≤181 x 10^9/L
AST	>48 IU/L
Triglycerides	>156 mg/dL
Fibrinogen	≤360 mg/dL

AST - aspartate aminotransferase, MAS – macrophage activation syndrome, sJIA – juvenile rheumatoid arthritis

ment may reverse the disease course. In active EBV infection, treatment with rituximab is also an option.[58] Increased immunosuppression for the underlying disease may be useful for rheumatologic patients with MAS.

For acutely ill patients, induction therapy consists of a series of weekly treatments with dexamethasone and etoposide and, possibly, the addition of cyclosporine.[48, 55,57] In patients with liver failure, treatment with alemtuzumab rather than etoposide may be preferable due to concerns of hepatotoxicity. Patients with central nervous system manifestations after 2 weeks of treatment might be eligible for intrathecal methotrexate and hydrocortisone treatment. Patients with lymphoma-associated HLH may benefit from cyclophosphamide, adriamycin, vincristine, and prednisolone (CHOP) chemotherapy in addition to etoposide.[59]

Etoposide use is a risk factor for development of acute myeloid leukemia and myelodysplastic syndromes in later life. To avoid these adverse effects, an alternative treatment option is intravenous immunoglobulin (IVIG) with or without glucocorticoids especially in patients with underlying rheumatologic diseases.[60] In critically ill patients with autoimmune diseases who develop MAS, cyclosporine and other immunosuppresants (e.g. anakinra) along with glucocorticoids are regularly chosen and etoposide is avoided. Anakinra an interleukin-1 antagonist, can also be used in those with sJIA-associated MAS.[61] There is also an ongoing phase II trial evaluating emapalumab (IFNγ blocking antibody) for MAS associated with sJIA.[62]

Guidelines do not exist for relapsed or refractory HLH. Patients with relapse, refractory, central nervous system disease or primary HLH are usually continued on standard protocol therapy until allogeneic hematopoietic cell transplantation is undertaken. The only available treatment option, other than clinical trials, is emapalumab plus dexamethasone with favorable efficacy and toxicity aspects.[63] Promising treatment options include a combination of doxorubicin, etoposide and glucocorticoids (DEP) as salvage therapy, the JAK2 inhibitor ruxolitinib and IL-6 blockade in patients with cytokine release syndrome (CRS), plasma exchange and splenectomy in patients with splenomegaly.[64-67] HLH remains a rare syndrome with poor prognosis despite early intervention. The reported overall mortality of HLH ranges from 20.4% to 88% in treated populations with variable baseline characteristics and length of follow up.[68] Survival is worse in patients with malignancy-associated HLH compared with patients with non–malignancy-associated HLH. Ferritin level > 50,000 is a poor predictor for 30-day mortality.[69] Of note, slower rates of decline in serum ferritin during treatment are a poor prognostic factor. Less than a 50% decrease during the first three weeks of therapy is associated with a higher mortality than a ferritin decrease ≥96%.[70]

CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME (CAPS)

CAPS is characterized by disseminated thrombotic vascular events in multiple organs in patients with underlying antiphospholipid syndrome (APS) leading to acute multi-organ failure.[71] Its prevalence in patients with APS is <1%, and it affects mainly women (72%) with a mean age of 39 years.[72] Recent surgery and infections are usual triggers in genetically predisposed patients. This condition has high morbidity and mortality (30-50%).

Patients present with almost simultaneous (within a week) multiple organ involvement and positive antiphospholipid antibodies. The clinical presentation depends on the affected organs and systems.[72] These include renal insufficiency and hypertension (kidney), ischemic ulcers, gangrene or livedo reticularis (skin), ischemic cerebrovascular events (brain), ischemic hepatitis (liver), acute respiratory failure from hemorrhage, pulmonary embolism or ARDS (lungs), myocardial infarction (heart). Typical laboratory findings include thrombocytopenia, hemolytic

Table 4. CAPS diagnostic criteria (All 4 required)

Multiorgan involvement (>3 organs/tissues/systems)
Synchronous clinical manifestations or within a week
Histopathological confirmation of small-vessel occlusion
Positive antiphospholipid antibodies

CAPS- catastrophic antiphospholipid syndrome

anemia and increased creatinine levels in the presence of antiphospholipid antibodies. Biopsy confirmation of thrombotic microangiopathy is required.

The diagnostic criteria for CAPS, as shown in **Table 4**, require the exclusion of other causes of multiple microthromboses.[73] The differential diagnosis includes disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), heparin-induced thrombocytopenia (HIT), sepsis, or systemic vasculitis.[73] CAPS should also be differentiated from HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets syndrome) in pregnant patients.

Hyperferritinemia was present in 71% of CAPS patients with mean levels higher than those seen in patients with APS alone (816 *vs.* 120 ng/mL). Approximately one third of CAPS patients had very high levels of ferritin (>1000 ng/mL).[74] Release of many pro-inflammatory cytokines, mainly IL-1, IL-6 and TNF from occluded micro-vessels during CAPS is the presumed pathogenetic mechanism leading to non-thrombotic manifestations such as ARDS.

Treatment of CAPS is directed at preventing further thrombosis with anticoagulation (heparin), removal of pathogenic anti-phospholipid antibodies with plasma exchange and cytokine cascade suppression with immunemodulatory/suppressive therapies such as systemic glucocorticoids, cyclophosphamide or IVIG.[75] When suspecting acute infection, appropriate antibiotics should be given.

In patients with CAPS resistant to first-line therapy, treatment with rituximab or eculizumab may have positive outcomes.[72,76,77] It has been shown that activation of complement is required for APS to develop in mouse models.[78] C5a interaction with its receptor results in inflammation, placental insufficiency, and thrombosis. Moreover, in these models, anti-C5 antibody (same mechanism of action as eculizumab) prevent pregnancy loss and thrombosis.

In terms of prognosis, triple therapy with therapeutic anticoagulation, glucocorticoids, plasma exchange and/or IVIG resulted in a higher chance of survival compared with no treatment or treatment with other regimens (adjusted OR = 9.7 and 1.7 respectively).[79]

SEPTIC SHOCK

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection.[80] Immune activation in response to infection causes the release of both pro-inflammatory and anti-inflammatory cytokines with variable clinical significance of both.

The clinical presentation of sepsis depends on the infectious cause, primary site of infection and the clinical features of immune response. Non-specific findings, such as abnormal vital signs, and altered mental status are common. In the skin, livedo reticularis can be observed. Regarding laboratory findings, elevated lactate levels (especially in septic shock), leukocytosis or leukopenia, elevated CRP and abnormal urinary and liver function tests can be seen.

Sepsis and septic shock with increased serum ferritin levels is observed more commonly in patients infected with DNA viruses, parasites, intracellular bacteria, fungi or in patients that have undergone transfusions or have suffered from hemolysis. Therefore, workup should be oriented more towards these causes. During infection, ferritin is produced by macrophages as a result of interleukin IL−1 and TNF-α induced nuclear factor kappa B (NF-κβ) activation.[81] As a result, further immune dysregulation is expected. Ferritin levels above 4420 ng/mL have been associated with an increase of IL-6, IL-18, INF-γ, and sCD163 and a decrease of the IL-10/TNF-α ratio, indicating a heightened pro-inflammatory response.[82]

Median serum ferritin levels of 371.5 ng/mL, 892.2 ng/mL, and 1784.9 ng/mL during the stages of sepsis, severe sepsis or septic shock, and multiple organ dysfunction syndrome (MODS), respectively, have been reported.[83] Ferritin levels have also been associated with higher mortality rate in pediatric patients with severe sepsis or septic shock.[84] Additionally, ferritin levels of septic pediatric patients in need of mechanical intubation for >48 hours were associated with disease severity.[85] Patients with elevated levels (≥300 ng/mL) had fewer hours off ventilation and required more inotropic medications.

In patients with influenza A infection, ferritin levels demonstrate a negative predictive value that might be useful in excluding the chance of developing serious complications. Levels ≥500 ng/mL show sensitivity of 57% and specificity of 83%, which could go up to 95% if the ferritin level cut-off was >955 ng/mL, for serious complications.[86]

Sepsis and septic shock treatment in general, consists of resuscitation measures with the use of intravenous fluids, vasopressors, oxygen therapy, possibly mechanical ventilation, and appropriate empirical antimicrobial therapy as well as rapid source control. However, in a state of elevated pro-inflammatory response, like the one in hyperferritinemic patients, further medications may be needed.[82] There remains uncertainty regarding the use of glucocorticoids in sepsis and septic shock. Glucocorti-

coids may counteract the excessive pro-inflammatory response present in sepsis. Part of the immune dysregulation in sepsis is also the dysfunction of the hypothalamic–pituitary–adrenal axis and glucocorticoid resistance in tissue.[87] Trials of glucocorticoid treatment have reported contradicting data regarding 90-day mortality.[88] For hyperferritinemic sepsis, however, increased survival rates are seen in patients with septic shock treated with glucocorticoids (methylprednisolone), IVIG, plasma exchange.[89] Anakinra has been tested in septic patients with features of MAS.[61] Treatment with anakinra was associated with a higher rate of 28-day survival (65.4%) compared with placebo (35.3%).

ADULT-ONSET STILL'S DISEASE (AOSD)

AOSD is a rare inflammatory condition that is considered to be autoimmune in origin, although the true pathophysiology remains elusive.[90] Current suggestions towards the etiology include macrophage activation and Th1 cytokines.[90] The incidence is estimated to be less than 1:100,000 individuals in the United States.[91] A rare clinical diagnosis of exclusion, the hallmarks of AOSD include quotidian fever, polyarthritis, and a mixed erythematous or salmon-colored maculopapular, patchy rash that covers the extremities and trunk.[90-92] Although not universal, sore throat and general arthralgias are extremely common. Systemic symptoms, particularly fever, are typically found.[91] AOSD accounts for up to 20% of fevers of unknown origin.[91,92] Lymphadenopathy, particularly cervical lymphadenopathy, is common. Lymph nodes in AOSD are often avidly enhancing on 18FDG-PET scans. A clinician might expect to find hepatosplenomegaly.[90-92]

In addition, on laboratory studies, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are uniformly elevated. LFT abnormalities and anemia of inflammation are common findings. Significant leukocytosis (e.g., >15,000/mm^3) may be found with neutrophilic predominance. AOSD will often present with negative ANA and RF labs, if obtained. Ferritin is typically elevated as well; one retrospective review of 57 patients revealed a mean ferritin of 8745 (range 84-130,000). Elevated serum ferritin levels higher than five times the upper limits of normal if combined w/ a decrease in the proportion of glycostylated ferritin (<20%) increase the specificity of AOSD to 93%.[90-92]

The Yamaguchi criteria are the most commonly used criteria for diagnosis (**Table 5**).[93] Notably, hyperferritinemia is absent. In addition, the disease is further classified among the three following categories: a monocyclic pattern, a polycyclic pattern where flares last < 1 year each, and a chronic pattern.[90]

Despite multiple complications from AOSD flares, prognosis is generally good, with an estimated mortality from AOSD itself being approximately 16% of affected individuals, typically due to transformation to the MAS.[90,92] First-line treatments remain empiric and consist primarily of glucocorticoids.[90-92] Methotrexate is a second-line treatment. Multiple trials are ongoing to examine the role of individual biologic anti-cytokine therapies, in particular IL-1, IL-18, and TNF-a.[90] In 2020, the FDA approved canakinumab, an IL-1 inhibitor, and the first agent approved specifically to treat AOSD.[94]

Table 5. Yamaguchi criteria. (To diagnose AOSD, at least five (5) of the criteria must be met, with at least two (2) coming from the major criteria)

Major Criteria	Minor Criteria
Fever >39C for >1 week	Sore throat
Arthralgia/arthritis >2 weeks	Recent onset lymphadenopathy
Typical salmon evanescent rash	Hepatosplenomegaly
Leukocytosis >10,000/mm^3 with >80% polymorphonuclear cells	Negative serum ANA or RF
	Abnormal liver function tests

ANA – antinuclear antigen, RF – rheumatoid factor

MULTI-SYSTEM INFLAMMATORY SYNDROME OF COVID-19 (MIS)

The COVID-19 pandemic has demonstrated the appearance of MIS, a new Kawasaki-like syndrome that affects primarily children and adolescents exposed to SARS-CoV-2, the virus that causes COVID-19, and who have typically resolved infection, up to several weeks after exposure. Its exact etiology is unknown, but it is hypothesized that it represents a hyper-immune response by the immature immune systems of these individuals to SARS-CoV-2 antigens.[95,96] Due to the novelty of this condition, its incidence is unknown.[96]

MIS-A, occuring in adults, is assumed to be a distinct clinical entity with increased severity and co-morbidities, but it is otherwise similar in presentation, management, and laboratory studies to MIS-C.[96] For example, diagnostic criteria for MIS-A include severe acute cardiac illness or dysfunction and encephalopathy, which may be seen in MIS-C with less severity.

Patient presentation for MIS-C/A uniformly includes fever. Exposure to SARS-CoV-2 might not be evident by history alone, and patients very often have positive antibodies to this virus. Cardiac involvement at presentation is typical, with tachycardia and hypotension being the most common presenting pathophysiologic manifestations.[97] Respiratory distress may occur as the disease progresses but has not been found to be the primary initial manifestation in most cases. Patients often present with acute gastrointestinal symptoms, rash and mucocutaneous injection, including the conjunctiva as seen in Kawasaki's disease.

Laboratory findings for MIS-C/A include elevated CRP and often elevated ESR. The patient will usually have a mild hyponatremia and leukopenia. Signs of coagulopathy (specifically elevated D-dimer and increased PT/INR, PTT) will be seen. Other inflammatory markers, such as procalcitonin and ferritin, are elevated in a majority of cases.[95-97] Cases typically present with a serum ferritin >10,000 ng/dL, but the prognostic value is unclear.[98]

MIS-C/A typically requires ICU admission. IVIG is the treatment of choice, and glucocorticoids are often used in conjunction. Infliximab (TNFa), anakinra (IL-1), and IL-6 inhibitors have also been used with less frequency and less success.[96] Despite the severity of the condition, with treatment the mortality of MIS-C is approximately 1.5%.[95] Cardiology follow-up is warranted when cardiac involvement is present.[97]

OTHER CAUSES OF HYPERFERRITINEMIA

As ferritin is a marker of acute inflammation, markedly elevated ferritin levels >1000 ng/dL may be seen, occasionally and intermittently, in a variety of other conditions, particularly in acute phases. However, and by contrast to the aforementioned syndromes, conditions where hyperferritinemia might be found are not characterized as hyperferritinemic syndromes.

Lymphomas might demonstrate hyperferritinemia, and some research has indicated that higher levels of ferritin at diagnosis correlate with worse prognosis.[99] Hyperferritinemia may be seen in liver disease.[100,101] Ferritin is stored in hepatocytes, and as such, elevated ferritin might be considered a marker of hepatic necrosis. In addition to diseases of hepatocyte injury and destruction, hereditary hemochromatosis, the familial disease of iron overload, can be characterized by ferritin levels >1000 ng/dL when not regularly treated with phlebotomy.[101]

DISCUSSION

The hyperferritinemic syndromes are characterized by definition as having serum ferritin levels elevated to >500 ng/dL being a reliable, characteristic finding of the syndrome.[15] Though limited in number, the hyperferritinemic syndromes represent diseases across a wide swath of medical and pediatric specialties. The central tenet is that hyperferritinemic syndromes are syndromes of intense systemic inflammation. Hence, the serum ferritin is often elevated above 1,000 ng/dL in these syndromes and may occasionally be elevated above 10,000 ng/dL.[47]

The unifying thread is that each syndrome is marked by severe inflammation and that treatment is based upon addressing the underlying cause or when that is unknown, targeting the immune system through various treatment modalities.

A new hyperferritinemic syndrome has emerged in the COVID-19 pandemic, MIS-C/A, and in must be considered in the context of the other hyperferritinemic syndromes: HLH, cAPS, AOSD, and septic shock. Significant advancement has been made in the development of disease-directed therapy in the last decade, but curative disease-specific treatment remains elusive.[62,63,72] What's more, it has been suggested that high levels of ferritin may play a role in disease pathogenesis, thus understanding the pathologic response to one syndrome may lead to better management of all.[15]

More studies are needed to elucidate the common role of ferritin in the pathogenesis of these syndromes or as a prognostic indicator for these syndromes, if any such role exists. Furthermore, clinicians should remember that ferritin is an acute phase reactant and should consider it alongside ESR and CRP to both diagnose and monitor response to treatment in specific inflammatory syndromes.

CONCLUSION

Hyperferritinemic syndromes are rare diseases that are challenging to diagnose and treat. MIS-A/C, hyperinflammatory complications of COVID-19 should be added to the hyperferritinemic syndromes. High levels of ferritin help with diagnosis and provide information about prognosis. Immunomodulatory treatment, including corticosteroids, are useful in all hyperferritinemic syndromes because of the noted heightened pro-inflammatory response. Additional treatment regimens depend on the underlying cause and disease severity. The proposed association of high levels of ferritin with disease pathogenesis needs further assessment in order to improve patient outcomes.

Disclosures/Conflicts of Interest

The authors have no conflicts of interest to disclose.

Funding

None

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