



'F' for 'F'erritin, 'F'ibrinogen

Ferritin

Initially considered as a protein important in iron metabolism and homeostasis, to being identified as elevated in acute infectious diseases, and then as a marker of acute inflammation followed by elucidation of its role in chronic inflammatory and auto-immune diseases (hyperferritinemia- the iron sword of auto-immunity), the humble serum ferritin has come a long way indeed. During the COVID-19 pandemic hyperferritinemia became the buzzword and serum ferritin served as a marker of severity of illness.

What is serum ferritin?

- Crystallizable protein with 35% ferric oxide hydroxide
- An acute phase reactant synthesized by the liver

What factors determine its levels?

- Intracellular iron levels- serum ferritin levels fall when levels are low and increase when iron levels are high
- IL-6, IL-1-beta and TNF alpha also increase the secretion of ferritin, hence elevated in inflammatory states and autoimmune conditions
- Also regulated by oxidative stress, thyroid, insulin, growth factors, second messengers, hypoxia-ischemia and hyperoxia

How does it act as an acute phase reactant?

It sequesters and stores iron intra-cellularly, thus reducing iron availability for oxygen radicals and prevents free radical damage that occurs in infection or inflammation.

Hyperferritinemia (serum ferritin > 500 ng/ml)

Serum ferritin becomes not just a marker of inflammation, but is a prognostic indicator and marker of severity of illness. Higher the levels, more the inflammation and risk for multi organ failure.

What are the Infections in which serum ferritin levels are high?

- a. Septic shock
- b. Bacterial infections
- c. Some viral infections- Dengue , Influenza A, H1N1, EBV, HIV, COVID-19
- d. Mycoplasma, Legionella pneumonia
- e. Tuberculosis

Which are the auto-immune conditions in which serum ferritin is elevated?

- a. Systemic onset juvenile idiopathic arthritis (SJIA)
- b. Systemic lupus erythematosus
- c. Rheumatoid factor positive polyarticular JIA
- d. Juvenile dermatomyositis (JDM)
- e. Macrophage activation syndrome (MAS) –
 - This is the term given to Hemophagocytic lymphohistiocytosis (HLH) seen in rheumatic diseases. MAS is most common in SJIA, but can occur in Kawasaki disease, SLE, JDM too.
 - Serum ferritin level >684ng/ml is one of the obligatory criteria for diagnosis of MAS in SJIA.
- f. Catastrophic Anti-phospholipid antibody syndrome(CAPS)

✓ Serum ferritin levels >5000 ng/ml is often suggestive of a MAS like condition and values above 10000ng/ml is highly likely to be a MAS/HLH like condition .

✓ In addition, serum ferritin/ESR ratio (value >21.5) is more useful than serum ferritin alone to differentiate SJIA-MAS from flare of SJIA.

Other conditions associated with high serum ferritin:

- a. Obesity
- b. Malignancy
- c. Iron overload

When should one order a serum ferritin in pediatric practice?

a. The most common scenario to send serum ferritin levels is a child with pyrexia of unknown origin with increasing toxicity and multi-organ dysfunction, dropping counts, increasing CRP and a dropping ESR. This may suggest an onset of potential macrophage activation syndrome.

The other conditions where it may be sent include

- b. Suspected flare of Systemic JIA
- c. Suspected MAS in a child with known rheumatic disease such as SJIA or SLE
- d. Kawasaki disease (if complicated with MAS), immunosuppression with IV methylprednisolone maybe considered along with IVIg

Fibrinogen

What is serum Fibrinogen ?

- Acute phase reactant plasma protein synthesized by the liver, physiological levels 2-4 g/L in healthy individuals
- Half-life of 3-5 days

Pro-inflammatory role of fibrinogen:

- Levels increase in inflammation due to increased synthesis and release by the cytokines (mainly Il-6) on hepatocytes
- Fibrinogen increases inflammatory activity of macrophages by binding to Toll-like receptor 4 (TLR4), causing increased secretion of TNF α , Il-6 etc.

✓ Degradation of fibrinogen by plasmin leads to Fibrin Degradation Products (FDP) and D-dimers which are again increased in high inflammatory states such as systemic arthritis, rheumatoid arthritis and correlate with disease activity.

High serum fibrinogen levels

1. Inflammatory arthritis, particularly Systemic onset JIA and Rheumatoid factor positive polyarticular juvenile idiopathic arthritis
2. Inflammatory bowel disease

Low serum fibrinogen levels

MAS (term used for HLH secondary to rheumatic diseases) - A consumptive coagulopathy which leads to fall in serum fibrinogen levels and rise in FDPs and D-dimer levels. In SJIA with MAS, the child has persistent fever, rash, and arthritis.

- ✓ *The trend of falling ESR and serum fibrinogen levels along with cytopenias and rise in CRP, serum ferritin, transaminitis is characteristic. It is prudent not to wait till absolute value falls <1.5 mg/dl and to look at serial values. ESR reflects serum fibrinogen level in the blood and can be done easily.*
- ✓ *Hence the “modified HLH criteria” for MAS should be applied in Systemic arthritis.*
- ✓ *Do not send only ferritin as a part of MAS/HLH workup .Always send the full workup (CBC,ESR,CRP, LFT, Ferritin ,Fibrinogen ,LDH and serum Triglycerides)all at the same time as the process is dynamic and follows a varied rate of elevation and reduction.*

Differences in criteria for HLH and MAS

HLH CRITERIA (2004)

Molecular diagnosis

Or

5/8 of the following:

- Fever ≥ 38.5 °C
- Splenomegaly
- Cytopenias in 2/3 lines
- Hgb < 9 g/dL
- Plts $< 100 \times 10^3$ /mL
- Neutrophils $< 1 \times 10^3$ /mL
- TG ≥ 265 mg/dL and/or
- Fibrinogen ≤ 150 mg/dL
- Hemophagocytosis
- Low NK cell function
- Ferritin ≥ 500 ng/mL

Elevated sIL-2 receptor

2016 Classification criteria for MAS in SJIA

Fever in SJIA patient

Serum

Ferritin > 684 ng/ml AND

2/4 Criteria:

Plts $< 181 \times 10^3$ /mL

AST > 48 u/L

TG > 156 mg/dL

Fibrinogen ≤ 360 mg/dL

Take Home Messages

- Clinical setting of persistent infection /infection associated inflammation /Severe inflammation warrants sending Ferritin and Fibrinogen
- Ferritin and fibrinogen are positive acute phase markers of inflammation.
- It is advisable to send both at the same time for better interpretation .
- ESR is a surrogate marker reflecting serum fibrinogen levels.
- Beware of a normal /low fibrinogen in a sick child (MAS) .
- Perform a full MAS workup whenever in doubt .(No restriction to ferritin alone)
- Interpreting of ferritin n fibrinogen in the context of inflammation and HLH/MAS is important .

	HB	WBC	Plts	CRP	ESR	Ferritin	Fibrinogen
Inflammation (Rheum cause)	Low	Usually, High	Usually, High	High	High	High	High
MAS/HLH	Low	Low	Low	Very High	Low	Very High	Low

NEXT COMING- “ G” for Glucocorticoids

Suggested reading

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