

The Hyperferritinemic Syndrome

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Ferritin is an iron-binding molecule that stores iron in a biologically available form. It also plays a role in numerous other conditions, including inflammatory, neurodegenerative and malignant diseases. Most clinicians dealing with inflammatory diseases perceive serum ferritin levels as a non-specific marker of the acute-phase response. Despite increasing evidence that circulating ferritin levels indeed reflect an acute-phase response, how and why serum ferritin is elevated is not yet known [1]. Circulating ferritin levels also play a critical role in inflammation. The expression of ferritin is regulated not only by the cytoplasmic amount of iron, but also by cytokines, oxidative stress, hormones and lipopolysaccharide, among others [2].

Over the last few years, accumulating data have implicated a role for ferritin as a signaling molecule and direct mediator of the immune system. This molecule can be either immunosuppressive or pro-inflammatory. The immunosuppressive effect is well known and seems to play a role in the development of autoimmune diseases. Different mechanisms may inhibit the ferritin-mediated suppression of the immune cells, and in turn, this impaired immunosuppression may favor the loss of tolerance and the development of autoimmune diseases [3]. The autoimmune diseases associated with hyperferritinemia include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), multiple sclerosis (MS) and antiphospholipid syndrome (APS) [2,4,5]. Yet, autoantibodies against ferritin are also associated with different autoimmune diseases [1]. Hyperferritinemia is also linked to several inflammatory conditions such as sepsis, systemic inflammatory response syndrome (SIRS), multiorgan dysfunction syndrome (MODS), macrophage activation syndrome (MAS), and the catastrophic variant of the antiphospholipid syndrome (CAPS) [6,7]. Furthermore, in critically ill patients, hyperferritinemia is associated with the severity of the underlying disease [6].

On the other hand, it has been proposed that ferritin can also be a pro-inflammatory signaling molecule [8]. There seems to be a complex interaction between ferritin and cytokines in the

control of pro-inflammatory and anti-inflammatory mediators. Pro-inflammatory cytokines can induce ferritin expression; in turn, ferritin may induce the expression of pro-inflammatory cytokines. Moreover, ferritin induction of anti-inflammatory cytokines (interleukin-10) is an important mechanism underlying the immunosuppressive effects of ferritin [1].

So, ferritin can be either an immunosuppressive or a pro-inflammatory molecule. These opposing effects are probably dependent on the activation of different pathways, through different receptors, possibly employing different effectors (i.e., L- versus H-ferritin), and possibly different contexts. Actually, this last idea resembles the “two-hit hypothesis”; for instance, for the high levels of ferritin to be pathogenic a second hit may be necessary, like a pro-inflammatory environment, a specific genetic background or even an infectious agent [1].

Four clinical conditions may be associated with high ferritin levels: MAS, adult-onset Still's disease (AOSD), CAPS, and septic shock [9]. These disorders are characterized by life-threatening hyperinflammation with high levels of ferritin and a cytokinetic storm, clinically presented as multiorgan failure. They share similar clinical signs, symptoms and laboratory parameters [1]. In addition, they also respond to similar therapies. In all conditions there is a good response to treatment with corticosteroids, plasma exchange and intravenous immunoglobulin G (IVIg), supporting a common pathogenic mechanism, and ferritin may be the link between them. It was previously shown that ferritin levels decreased gradually after each plasma exchange session. Furthermore, IVIg may be relevant not only because antibodies against ferritin may be present, but IVIg may also prevent the release of pro-inflammatory cytokines. Macrophages seem to be major players in these four conditions. They are responsible for the production of cytokines and also appear to be extremely important in the production and secretion of serum ferritin [1,10]. We hypothesize that the hyperferritinemia seen in these clinical conditions is part of the pathogenic mechanism and not merely a secondary product of the inflammatory process. Probably, in an inflammatory environment as observed in these diseases, the grossly high levels of ferritin may be involved in some sort of loop mechanism where ferritin's inflammatory properties are exacerbated, leading to an extreme expression of additional inflammatory mediators [1]. Still, not all patients with these clinical conditions have hyperferritinemia; indeed, in about 10% of AOSD patients the

ferritin levels are normal. Perhaps in this subgroup of patients the disease has a different etiology with a different pathogenesis. However, there are other diseases characterized by high levels of ferritin that do not have an inflammatory response, such as hyperferritinemia-cataract syndrome [1].

This concept of hyperferritinemia as a major contributor in the pathogenesis of these conditions may be extremely relevant when considering more targeted therapy. In order to recall the importance of this concept, we propose to include these clinical conditions under a single classification: “The Hyperferritinemic Syndrome.”

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