Ferritin and Severe COVID-19, from Clinical Observations to Pathogenic Implications and Therapeutic Perspectives

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ABSTRACT A virally-induced cytokine storm syndrome, associated with a massive and overwhelming systemic inflammation, burdens a subgroup of patients with severe coronavirus disease-2019 (COVID-19), which leads to pulmonary inflammation and extensive lung damage. These severe COVID-19 patients are characterized by high ferritin levels. These findings mirror what was previously reported about the prognostic role of this iron storage protein in other inflammatory diseases included in the hyperferritinemic syndrome. The latter suggests that ferritin could be a further pathogenic mediator in enhancing the inflammatory process, stimulating inflammatory pathways, and thus perpetuating a vicious pathogenic loop. Considering its activity as an immune activator, a therapeutic approach targeting ferritin may be also postulated in these diseases. Considering these observations, high ferritin levels characterize severe COVID-19 and other diseases included in the hyperferritinemic syndrome. Because ferritin could enhance the inflammatory process, it could be tested as a possible new therapeutic target to improve the outcome of these patients.

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KEY WORDS: coronavirus-19 (COVID-19), ferritin, hyperferritinemic syndrome

The coronavirus disease-2019 (COVID-19) has recently highlighted the role of systemic hyper-inflammation as a major cause of death [1,2]. A virally-induced cytokine storm syndrome, associated with a massive and overwhelming systemic inflammation, burdens a subgroup of patients with severe COVID-19. which leads to pulmonary inflammation and extensive lung damage [1,2]. These severe COVID-19 patients are characterized by high ferritin levels [3,4], as also shown in the work by Dahan et al., in this issue of the *Israel Medical Association Journal* [5]. The authors described a significant increase of ferritin levels in severe COVID-19 patients (2817.6 ng/ml) when compared with those codified as non-severe (708.6 ng/ml) [5].

These findings mirror what was previously reported about the prognostic role of this iron storage protein in other inflammatory diseases [6,7]. In fact, in adult onset Still's disease (AOSD), higher levels of ferritin are associated with the occurrence of macrophage activation syndrome (MAS), the most common life-threatening complication for these patients [6,8]. Furthermore, in MAS patients, high levels of ferritin are associated with mortality [9]. Similarly, in sepsis, high ferritin levels identify more severe patients who are at high risk of poor prognosis [10,11].

This association between high ferritin levels and a more aggressive subset of these diseases may suggest a possible pathogenic role of this molecule, as proposed by the concept of the hyperferritinemic syndrome [12]. The latter comprises four inflammatory diseases–AOSD, MAS, sepsis, and catastrophic anti-phospholipid syndrome–and this syndrome suggests that ferritin could be a further pathogenic mediator in enhancing the inflammatory process [12]. In fact, its production by liver and macrophages is enhanced by the inflammatory process since ferritin transcription is elicited by interleukin (IL)-1β, IL-6, and interferon (IFN)-γ, which upregulate the ferritin gene transcription through the increased binding of nuclear factor-κB (NF-κB) to FER2 upstream of the iron responsive element and coding region [13,14]. After that, independently of its iron content, ferritin may stimulate intracellular inflammatory pathways culminating in activation of NF-κB [14]. Thus, the final result of ferritin stimulation is the increased expression of pro-inflammatory mediators such as IL-1β and inducible nitric oxide synthase [14].

In this context, both subunits, which compose ferritin heavy (FeH) and light (FeL) subunits, have been studied due to their possible inflammatory activities [15]. Interestingly, in affected tissues of AOSD and MAS, FeH and FeH+/IL-12+ macrophages are highly represented in inflammatory infiltrate, suggesting a possible pathogenic role [16,17]. It has been shown that inflammatory stimuli preferentially induce the release of FeH, which binds a specific receptor on immune cells, namely the T-cell immunoglobulin and mucin domain (TIM)-1 in humans and TIM-2 in rodents [18,19]. In addition, the inflammatory properties of FeH

were noted in an experimental model of sepsis [20]. In this work, the deletion of FeH induced an impaired activation of NF-κB and a reduced production of IL-1β, IL-6, IL-12, and IFN-γ [20].

Recently, a significant effect of FeH on human macrophages has been shown via the activation of NLRP3 inflammosome and consequent synthesis of pro-inflammatory molecules [21]. The researchers showed that stimulation with FeH may induce an increased expression and release of IL-1β and IL-12 on human macrophages [21]. In addition, paralleling with IL-1β, FeH may lead to a significant expression of NLRP3, a cytosolic innate immune signaling receptor, which is the main factor associated with the maturation and production of this cytokine, thus suggesting a vicious cycle perpetuated by FeH, IL-1β and NLRP3 [21]. Considering all these observations, it is possible to speculate that ferritin may stimulate inflammatory pathways, acting as an enhancer of the inflammatory process in severe COVID-19 as observed in other inflammatory disease (e.g., AOSD, MAS, sepsis) [22,23]. Thus, severe COVID-19 could potentially be considered another piece of the puzzle of the hyperferritinemic syndrome [24].

Due to its reported activity as an immune activator, a therapeutic approach targeting ferritin may be postulated in these inflammatory diseases [25], including severe COVID-19. In this context, plasma exchange (PE), high-volume hemofiltration (HVHF), and desferrioxamine, have been already tested [26-28]; whereas, other therapeutic options could be specifically developed in the future for clinical application, such as monoclonal antibodies targeting ferritin or its specific subunit. PE and HVHF have been used to treat MAS and sepsis by mechanically removing toxins and inflammatory mediators [26,27]. Their effectiveness in reducing ferritin is very high. Despite promising results, a careful selection of patients is necessary due to the cardiovascular burden of these procedures in patients affected by a cytokine storm syndrome [26,27].

Desferrioxamine, an iron chelator, has been tested in the experimental model of atherosclerosis [28]. It may inhibit lipopolysaccharide-induced increases of soluble cellular adhesion molecules and monocyte chemoattractant protein-1 in serum. Furthermore, this drug activates the redox-sensitive transcription factors, NF-κB and activator protein-1 in the aorta [28]. Interestingly, these pathways are the same that are elicited by ferritin, further reinforcing the role of ferritin as immune mediator [13-15]. However, although desferrioxamine effectively reduces ferritin levels, a concern has been raised due to the increased rate of severe infections in patients treated with iron chelators [29].

Alternatively, it is possible to target the products of downstream pro-inflammatory cascades stimulated by ferritin. Based on these observations, many clinical studies are ongoing to assess the efficacy of IL-1, IL-6, and IFN-γ inhibition on severe COVID-19 (NCT04317092, NCT04310228, NCT04332913, NCT04324021, NCT04339712, NCT04330638). In addition, considering that these pro-inflammatory pathways converge on NF-κB, inhibitors of these factors are being tested in inflammatory diseases and may have a therapeutic potential in this setting [30-33].

CONCLUSIONS

High ferritin levels characterize severe COVID-19 and other diseases included in the hyperferritinemic syndrome. Because ferritin could enhance the inflammatory process, it could be tested as a possible new therapeutic target to improve the outcome of patients who are affected by either severe COVID-19 or diseases included in the hyperferritinemic syndrome.

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Capsule

Keeping the lid on infection spread

From February to April 2020, many countries introduced variations on social distancing measures to slow the ravages of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Publicly available data show that Germany has been particularly successful in minimizing death rates. **Dehning** and co-authors quantified three governmental interventions introduced to control the outbreak. The authors predicted that the third governmental intervention–a strict contact ban since 22 March–switched incidence from growth to decay. They emphasize that relaxation of controls must be done carefully, not only because there is a 2-week lag between a measure being enacted and the effect on case reports but also because the three measures used in Germany only just kept virus spread below the growth threshold.

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Capsule

COVID-19 pandemic in France

Coronavirus disease-2019 (COVID-19) exacted a heavy toll in France during March and April 2020. Quarantine measures were effective in reducing transmission by 84%, and some relaxation of social isolation was expected in May. **Salje** et al. fit transmission models for the epidemic in France to hospital admissions. The authors forecast that 2.9 million people will have been infected by 11 May, representing 4.4% of the population–a value inadequate for herd immunity. Daily critical care hospitalizations should reduce from several hundreds to tens of cases, but control will remain a delicate balancing act. Any relaxation of lockdown in France will have to be carefully controlled and monitored to avoid undermining more optimistic forecasts.

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