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Editorial

# Ferritin and myalgic encephalomyelitis/chronic fatigue syndrome in post COVID-19, an unexpected facet of the hyperferritinemic syndrome?

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Coronavirus disease 2019 (COVID-19) has provoked a catastrophic medical emergency worldwide [1]. In the course of time from the beginning of this pandemic, subacute and long-term effects in patients suffering from COVID-19 have been increasingly recognised [1,2]. Thus, the term "long-COVID-19" has been proposed to describe this collection of signs and symptoms which may continue or sometimes develop following the SARS-CoV-2 infection. The latter is defined as post-COVID-19 syndrome [3]. In a large percentage of these patients, mental health problems and fibromyalgia have been also recognised [3–5]. Interestingly, many patients could experience severe fatigue in a clinical setting of myalgic encephalitis/chronic fatigue syndrome (ME/CFS), even several months after SARS-CoV-2 infection [6]. In this context, low level inflammation and hypoperfusion have been recently proposed as potential pathomechanisms of occurrence of ME/CFS [7]. On these bases, possible predictors of ME/CFS have been recently investigated in 234 patients with post-COVID-19 syndrome [8]. To date, almost 60% of evaluated patients had fatigue symptoms, and 21.4% met classification criteria for ME/CFS. The authors performed a deep assessment of laboratory features of included patients, stratifying the results in 3 groups, namely patients meeting classification criteria for ME/CFS, patients with fatigue but not reaching the classification criteria for ME/CFS, and patients without fatigue. Despite a moderate increase, patients with ME/CFS had significantly higher serum ferritin levels when compared with patients with fatigue not reaching the classification criteria and patients without fatigue. Interestingly, serum ferritin levels also correlated with the severity of the clinical picture, assessed by fatigue assessment scale and self-rating depression scale. Finally, serum ferritin levels were significantly higher in female patients with ME/CFS [8]. Interestingly, these results suggested how the burden of the inflammatory process in COVID-19 is associated with its psychological consequences. In fact, different steps contributing to neuropathology in COVID-19 are recognised and they may be grouped into overlapping mechanisms of direct viral infection, severe systemic inflammation, neuroinflammation, microvascular thrombosis and neurodegeneration [3]. All these alterations are directly correlated with the severity of the inflammatory process during COVID-19. In addition, the finding of the association between serum ferritin levels and ME/CFS is somewhat surprising as low, rather than high, values of this molecule have been historically associated with fatigue in both anaemic and non-anaemic individuals and iron supplementation may improve fatigue in more than 80% of iron deficient patients [9]. Similarly, low ferritin levels have been reported to be associated with fibromyalgia, and iron supplementation may improve fibromyalgia symptoms [10].

Taking together these observations, a possible link between inflammatory process, serum ferritin levels, and occurrence of ME/CFS in post-COVID-19 syndrome may be suggested, furtherly expanding the spectrum of the hyperferritinemic syndrome. The latter includes Still's disease, macrophage activation syndrome, and catastrophic antiphospholipid syndrome which are all characterized by marked serum ferritin levels [11]. Moreover, severe COVID-19, which may be similarly characterized by high serum ferritin levels, has been also considered as another piece of the puzzle of the hyperferritinemic syndrome [12]. Many markers are associated with the underlying inflammatory process, but high serum ferritin levels appear to be specific of these diseases thus suggesting its evaluation in their sequalae [13].

From a pathogenic point of view, a possible link between serum ferritin levels and ME/CSF in post-COVID-19 syndrome may be proposed. During the early phases of ME/CFS, the involvement of the immune system has been increasingly reported [14,15]. Actually, activated cytotoxic CD8 + T cells and poorly functioning NK cells have been pointed out in patients with ME/CSF [14,15]. These alterations may mirror what happens in the cytokine storm syndrome, which is similarly related to activated cytotoxic CD8 + T cells and poorly functioning NK cells [16]. Possibly, the different degree of the inflammatory burden may lead to a reduced immune response in ME/CFS in respect to the massive activation of the cytokine storm syndrome [16]. In this context,

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high serum ferritin levels may amplify the immune response in ME/CFS as proposed during the hyperferritinemic syndrome acting as a pro-inflammatory cytokine [13,17]. Once endocytosed, ferritin is able to stimulate some pro-inflammatory pathways activating NF-κB and producing pro-inflammatory cytokines [13,17]. Therefore, in the multifactorial aetiology of ME/CFS, high serum ferritin levels could contribute to the production of pro-inflammatory cytokines, especially in early phases of the disease [18]. Probably, these proinflammatory mechanisms of ferritin could have a further relevance in ME/CFS developing after an inflammatory condition as COVID-19. However, other mechanisms may be anticipated to contribute to the association between ME/CFS and serum ferritin levels. There is a well-known clinical and pathophysiological overlap between ME/CFS and depression as both diseases share inflammatory, oxidative and nitrosative pathways [19]. Interestingly, high ferritin levels have been reported in depressed patients [20]. Beyond inflammation, oxidative stress may represent a potential contributor to this association. Indeed, oxidative DNA damage has been reported in both patients with ME/CFS and depression [21]. Of note, in the general population, ferritin iron levels are associated with urinary 8-hydroxydeoxyguanosine (8-OHdG), a biomarker of systemic oxidative DNA damage and repair [22]. Iron released from ferritin may catalyse several reactions leading to the generation of activated oxygen species contributing to DNA damage [23].

In addition, the assessment of ferritin may provide useful information in clinical practice. The physicians could include its evaluation in the management of patients with post-COVID-19 syndrome [13]. High serum ferritin levels may be used as clinical feature to timely identify patients with ME/CSF. Consequently, an early recognition could improve the management of these patients by using a feasible biomarker, which is easily and widely used in clinical practice [24]. Patients with hyperferritinemic syndrome may have an impairment of quality of life even if they achieve a clinical remission [25]. Thus, a better management of the hyperferritinemic syndrome is advocated in ameliorating the outcomes of these patients, also considering ferritin and its elicited pathways as possible therapeutic target [26,27]. Finally, based on an enhanced knowledge of COVID-19 pathogenic mechanisms, a more tailored therapeutic strategy of these patients may be developed to improve the systemic manifestations, immunological dysregulations, complications, host-specific vulnerability, and long-term health consequences in these patients [28–30].

However, some limitations of ferritin measurement should be taken into consideration because of certain demographic and physical characteristics may alter iron homeostasis and may affect serum ferritin levels. Particularly, old age, obesity, liver diseases, and cancers may affect iron homeostasis thus reducing the usefulness of ferritin assessment. Therefore, additional studies are needed to fully elucidate the role of ferritin evaluation in this context of post-COVID-19 syndrome.

In conclusion, based on the evidence of post-COVID-19 syndrome and ME/CFS, the spectrum of the hyperferritinemic syndrome could be furtherly expanding. So far, high ferritin levels have been proposed to identify a subset of patients with inflammatory disease burdened by a hyper-inflammatory response leading to the occurrence of the cytokine storm syndrome. However, it is also possible that a moderate increase of serum ferritin levels may contribute to patients with post-COVID-19 syndrome to the occurrence of ME/CFS, enhancing the pro-inflammatory burden of disease pathogenesis or inducing oxidative DNA damage. Furthermore, the clinical relevance of ferritin evaluation could be suggested in identifying a more severe of these patients to be promptly managed. Finally, future specific designed studies are needed to fully elucidate these issues in improving the knowledge and the management of post-COVID-19 syndrome and ME/CFS.

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## Authors' contributions

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## Declaration of Competing Interest

The authors declare that they have no conflicts of interest for this work.

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Piero Ruscitti[a,*], Francesco Ursini[b,c], Yehuda Shoenfeld[d,e,f]
[a] *Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, delta 6 building, PO Box 67100, L'Aquila, Italy*
[b] *Medicine & Rheumatology Unit, IRCCS Istituto Ortopedico Rizzoli (IOR), 40136 Bologna, Italy*
[c] *Department of Biomedical and Neuromotor Sciences (DIBINEM), University of Bologna, 40125 Bologna, Italy*
[d] *Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel HaShomer 5265601, Israel*
[e] *Sackler Faculty of Medicine, Ariel University, Ariel 40700, Israel*
[f] *Laboratory of the Mosaic of Autoimmunity, Saint-Petersburg State University, 199034 St. Petersburg, Russia*

[*] Corresponding author.
*E-mail address:* piero.ruscitti@univaq.it (P. Ruscitti).