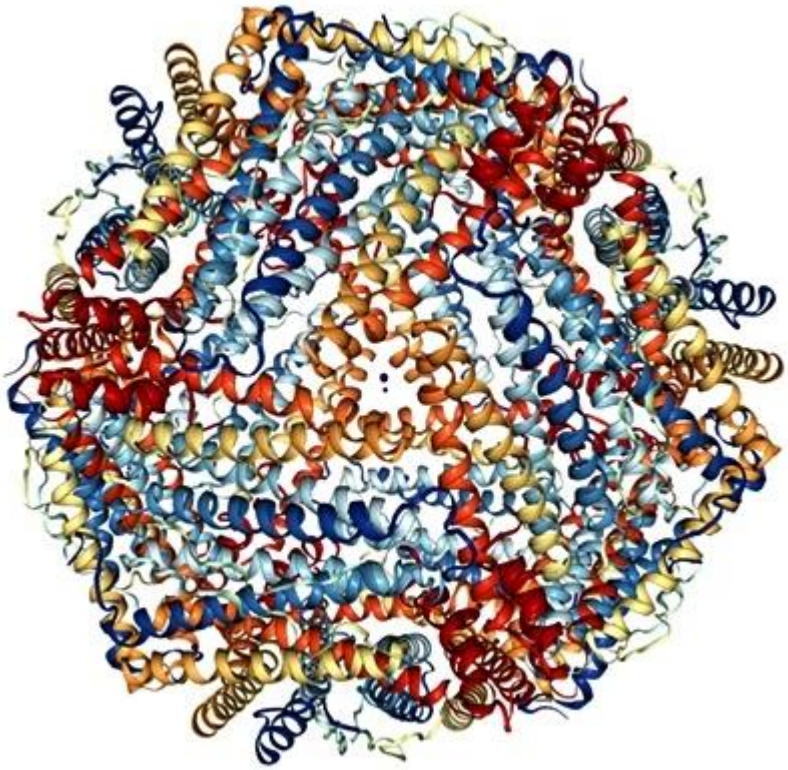
Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a multisystem neuroimmune disease characterized by neurological, immunological, gastrointestinal, and mitochondrial disorders. The criteria include a "substantial impairment or decrease in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities" for at least 6 months, accompanied by a profound fatigue that is not alleviated by rest, along with postexertional malaise, unrefreshing sleep, cognitive impairment, dysautonomia, especially postural orthostatic tachycardia syndrome (POTS), and altered pain and sensory perception. Infection with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) can lead to a new disease called long-COVID-19 or post-acute COVID-19 syndrome (PACS). Long/post-COVID syndrome represents a heterogeneous nosological entity, despite similar or overlapping symptoms between patients, and clear diagnostic criteria are yet to be established. Numerous recent studies have addressed the overlapping presentations between ME/CFS and long COVID. In this study, the Japanese authors examined the clinical and laboratory features of patients with long COVID who subsequently developed a clinical diagnosis of ME/CFS based on internationally standardized criteria. In their previous study, the same team of researchers found that the prevalence of ME/CFS following COVID-19 is 16.8%, which is significantly higher than the general population rate (less than 1%).

The pathogenesis of ME/CFS is not fully elucidated. Immune dysfunction is a key feature, and many symptoms suggest chronic immune activation. Biomedical findings include T-cell abnormalities, diminished function of natural killer (NK) cells, mitochondrial dysfunction, and vascular and endothelial abnormalities. Other findings include intolerance to exercise, reduced oxygen consumption, reduced anaerobic threshold, and abnormal metabolic profiles.

Ferritin is the major intracellular protein that stores iron in a soluble and nontoxic state in prokaryotes and eukaryotes. Hyperferritinemia is caused by inflammation, infectious diseases, hematological and malignant diseases, and liver and renal dysfunctions. Ferritin is composed of light-chain ferritin (L-ferritin), required for the long-term storage of iron, and heavy-chain ferritin (H-ferritin), with ferroxidase activity. The variation in subunit composition may affect the rates of iron uptake and release in different tissues. Defects in the light chain ferritin gene are associated with hyperferritinemia-cataract syndrome and neurodegeneration caused by brain iron accumulation. This disease is characterized by neuronal loss and gliosis, found in the cerebral cortex, thalamus, substantia nigra, caudate, putamen, globus pallidus, and cerebellum. Intranuclear and intracytoplasmic inclusion bodies stained positively for iron were observed in neurons, glia, and endothelial cells. Their

greatest density was detected in the putamen. Autoantibodies specific to ferritin light-chain polypeptide are frequently detected in patients with immune-related pancytopenia.

In 2021, Yapici-Eser et al. utilized a computational methodology to investigate mimicry between human proteins and SARS-CoV-2 proteins. They classified these interactions according to the molecular pathways of neuropsychiatric symptoms that developed in COVID-19. Interestingly, they found a mimicry of SARS-CoV-2 proteins (spike protein, NSP7, and papain-like protease, which is responsible for viral replication) with ferritin light chain protein. (Yapici-Eser et al. Neuropsychiatric Symptoms of COVID-19 Explained by SARS-CoV-2 Proteins' Mimicry of Human Protein. Front Hum Neurosci 2021 15:656313.) https://www.frontiersin.org/journals/human-neuroscience/articles/10.3389/fnhum.2021.656313/full



light-chain ferritin structure

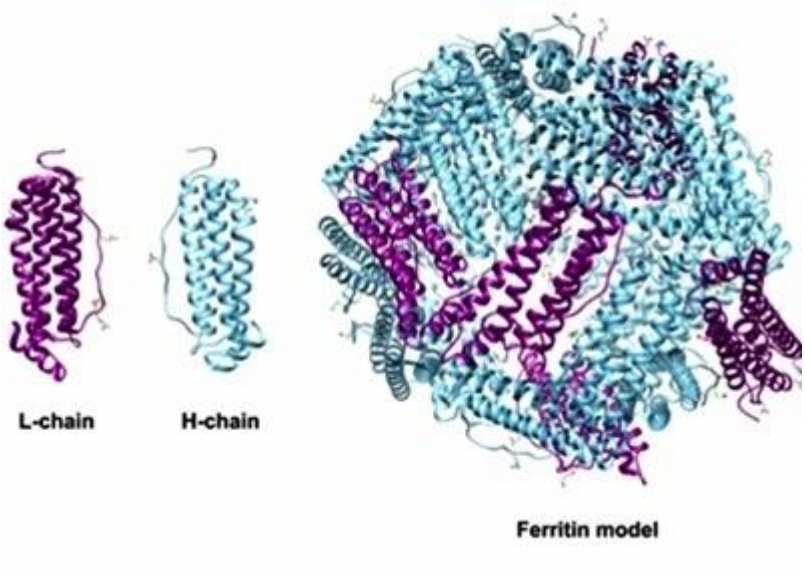
About the Study and Results

In this retrospective observational study, the authors examined the clinical and laboratory features of patients diagnosed with long COVID who subsequently developed a clinical diagnosis of ME/CFS based on internationally standardized criteria. They enrolled patients with persistent symptoms more than 4 weeks after COVID-19 onset, who were treated at the Long COVID clinic at Okayama University Hospital. Patients with long COVID did not have pre-existing hyperferritinemia.

234 participants were categorized into three groups: (1) patients with a clinical diagnosis of ME/CFS based on all of the three internationally standardized criteria, such as the Fukuda, the Canadian Consensus, and the Institute of Medicine (IOM) criteria (ME/CFS group), (2) individuals who experienced fatigue but did not meet the ME/CFS criteria (non-ME/CFS group), and (3) participants without fatigue (no-fatigue group). Of 234 patients, 59% (139 patients) complained of general fatigue, while 41% (95 patients) did not. Of 139 patients with fatigue, 40% (50 patients) met all three sets of diagnostic criteria for ME/CFS (Fukuda criteria, CCC, and IOM criteria). These 50 patients were included in the ME/CFS group. The remaining 89 patients who experienced fatigue but did not meet diagnostic criteria for ME/CFS, were included in the non-ME/CFS group.

Data on gender, age, body mass index, acute-phase severity, and time from COVID-19 onset to the first visit at the long COVID clinic were collected from the medical records. There was no significant difference in gender, age, BMI, and acute-phase treatment between the three groups.

At the first visit to the clinic, symptom severity was measured by the Fatigue Assessment Scale (FAS), EuroQol 5 Dimensions 5 Levels (EQ-5D-5L), the Self-Rating Depression Scale (SDS), and the Frequency Scale for Symptoms of Gastroesophageal Reflux Disease (FSSG). The scores for all self-rating scales (FAS, FAS physical, FAS mental, EQ-5D-5L, EQ-5D VAS, and SDS) were more severe in the ME/CFS group than in the other two groups.



Laboratory Data

Laboratory analysis included blood cell count, inflammatory or coagulation markers, biochemistry, and endocrine parameters: serum adrenocorticotropin (ACTH), cortisol, free thyroxin (FT4), thyrotropin (TSH), growth hormone (GH), and insulin-like growth factor (IGF)-I.

The levels of hemoglobin and inflammatory or coagulation markers did not differ among the three groups.

Patients with long COVID who subsequently developed ME/CFS (193.0 µg/L) had higher serum ferritin levels than patients with long COVID who did not meet the ME/CFS criteria (98.2 µg/L) and participants without fatigue (86.7 µg/L).

Serum ferritin levels were significantly higher in men (223.0 µg/L) than in women (50.3 µg/L).

However, women in the long COVID and ME/CFS group had higher serum ferritin levels (68.9 µg/L) than women in the non-ME/CFS group (43.8 µg/L). This difference was not observed in men. The authors emphasized that women are more likely to suffer from iron deficiency and have lower serum ferritin levels than men.

Serum ferritin levels correlated negatively with IGF-I levels in the ME/CFS group. This correlation was stronger in women.

The HPA axis function did not differ between the groups, according to similar serum levels

of FT4, cortisol, and ACTH, and ACTH/cortisol ratios. However, patients with long COVID and ME/CFS had higher serum TSH levels and lower FT4/TSH ratios than participants from the non-ME/CFS group. Also, in the long COVID and ME/CFS group, serum GH levels were lower than in the no-fatigue group (0.22 ng/mL *versus* 0.37 ng/mL).

Conclusion

This study found that patients with long COVID who developed ME/CFS based on all three internationally standardized criteria had elevated serum ferritin levels, identifying serum ferritin as a possible biomarker for detecting the transition to ME/CFS, especially in female patients. Endocrine workup further showed that long COVID patients who developed ME/CFS had higher serum TSH levels but lower growth hormone levels and that insulin-like growth factor-I levels correlated inversely with ferritin levels.

There is a possible link between the inflammatory process, serum ferritin levels, and the occurrence of ME/CFS in long COVID syndrome. It was suggested that a moderate increase of serum ferritin levels observed in long COVID syndrome could contribute to the occurrence of ME/CFS, enhancing the pro-inflammatory burden or inducing oxidative DNA damage. However, as hyperferritinemia was not accompanied by an increase in other inflammatory markers in this study, the authors concluded that persistent inflammation cannot explain the phenomenon of hyperferritinemia in long COVID syndrome.

Since a pathophysiological mechanism of hyperferritinemia in patients with long COVID who have developed ME/CFS remains hypothetical, the authors concluded that further studies are needed to understand ferritin metabolism in this patient group.

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Journal Reference

Yamamoto, Y.; Otsuka, Y.;Tokumasu, K, et al. Utility of Serum Ferritin for Predicting Myalgic Encephalomyelitis/Chronic Fatigue Syndrome in Patients with Long COVID. J. Clin.Med. 2023, 12, 4737. https://doi.org/10.3390/jcm12144737


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