Concept Paper

Potential Role of HFE-Mediated Iron Overload and Low Ferroxidase Activity in the Pathogenesis of Refractory SIBO and Autonomic Dysregulation

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Potential Role of HFE-Mediated Iron Overload and Low Ferroxidase Activity in the Pathogenesis of Refractory SIBO and Autonomic Dysregulation

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Abstract

Background: The clinical management of refractory Small Intestinal Bacterial Overgrowth (SIBO) and persistent gastrointestinal dysmotility represents a significant challenge, as these symptoms are often resistant to standard antibiotic treatments. While frequently categorized as functional disorders, the chronicity and systemic nature of these presentations suggest a possible underlying involvement of the autonomic nervous system. We explore the hypothesis that systemic iron dysregulation, rather than isolated dysbiosis, may contribute to these neuro and gastrointestinal manifestations. **Hypothesis:** We propose that iron overload mediated by HFE mutations, potentially exacerbated by low ferroxidase activity (ceruloplasmin), may lead to the accumulation of non-transferrin-bound iron (NTBI) in its reactive ferrous state (Fe2+). In this framework, we examine whether a lack of efficient iron chaperoning creates a pro-oxidative environment that could interfere with normal autonomic function. **Mechanism:** The suggested mechanism involves the Fenton reaction, where excess Fe2+ facilitates the generation of hydroxyl radicals. It is hypothesized that this localized oxidative stress may affect the unmyelinated neurons of the myenteric plexus, potentially leading to autonomic dysregulation. Such an environment could impair intestinal motility, thereby creating a substrate for recurrent and refractory SIBO. Furthermore, this iron dysregulation may act as a nutrient for pathogenic microbiota. This availability supports bacterial proliferation and biofilm formation, further contributing to the refractory nature of SIBO. **Clinical Relevance:** This model suggests that in patients with overlapping HFE variants and low ceruloplasmin, refractory SIBO may be a symptom of a broader metabolic dysregulation. Consequently, therapeutic strategies could consider the management of the systemic iron burden. Therapeutic phlebotomy is discussed as a potential intervention to reduce reactive iron levels, which might mitigate oxidative stress and support the stabilization of autonomic gastrointestinal function

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1. Introduction

Functional gastrointestinal disorders, particularly Irritable Bowel Syndrome (IBS) and Small Intestinal Bacterial Overgrowth (SIBO), are conventionally managed as localized dysbiosis or visceral hypersensitivity through antibiotics and dietary modifications.

However, a significant subset of patients presents with symptoms that are highly refractory and recurrent. In these cases, the clinical picture often suggests an underlying failure in gastrointestinal motility, potentially linked to a subtle autonomic neuropathy affecting the myenteric plexus. When such persistent neurogastrointestinal symptoms appear alongside systemic manifestations, investigating inborn or acquired errors of metabolism becomes interesting.

A key candidate for this systemic disruption is abnormal iron metabolism. While iron overload is typically studied in the context of organ damage (hemosiderosis), its potential role as a neurotoxic agent in the enteric nervous system remains under-explored. This paper proposes a mechanism

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where iron dysregulation, driven by **HFE gene mutations**, acts as a contributor to gastrointestinal dysautonomia.

Specifically, we hypothesize that the combination of increased iron absorption and compromised ferroxidase activity—evidenced by low ceruloplasmin levels—fails to safely sequester iron. This failure results in the generation of Non-Transferrin-Bound Iron (NTBI) in its highly reactive ferrous state (Fe2+). Through the Fenton reaction, this free iron may generate localized oxidative stress that interferes with the unmyelinated neurons of the enteric nervous system. Simultaneously, this surplus of bioavailable iron may act as a growth factor for pathogenic microbiota, facilitating bacterial proliferation and the formation of biofilms that resist standard antibiotic therapy. By shifting the focus from simple dysbiosis to iron-mediated oxidative neurotoxicity and metabolic microbial support, we may better understand the refractory nature of SIBO and its potential link to broader autonomic and inflammatory risks.

2. Clinical Observations and Pathophysiological Framework

2.1. Clinical Presentation and Family History

The hypothesis presented in this study is based on the clinical case of a proband with refractory SIBO and a multisystemic profile of autonomic dysregulation, characterized by palpitations, dizziness, nausea and periods of deep, overwhelming fatigue. These symptoms have proven resistant to standard functional treatments; Notably, such interventions often appear to exacerbate the patient's condition, likely by increasing the metabolic burden on a liver already compromised by oxidative stress.

Biochemical and genetic screenings of the proband revealed **heterozygosity for HFE gene mutations** and consistently **low levels of serum ceruloplasmin**.

Of particular clinical relevance is the proband's diagnosis of **cutaneous B-cell marginal zone lymphoma**. While specific causal studies in this patient have not been conducted, the existing literature suggests a potential link between chronic oxidative stress, iron-mediated immune dysregulation, and lymphoid proliferation.

2.2. The Diagnostic Gap

In a healthy physiological state, iron is strictly chaperoned by transferrin and oxidized by ceruloplasmin to prevent tissue damage. In this case, we hypothesize that the synergy between the HFE variant (increasing iron influx) and low ceruloplasmin (impairing iron sequestration) facilitates the emergence of **Non-Transferrin-Bound Iron (NTBI)**.

This reactive iron (Fe2+) can participate in the **Fenton reaction**, producing hydroxyl radicals (·OH) that target cellular lipids and proteins. We propose that the unmyelinated fibers of the autonomic nervous system, particularly those governing intestinal peristalsis, may be especially vulnerable to this localized oxidative environment. The resulting "functional" stasis would then provide the ideal substrate for bacterial overgrowth, explaining why antibiotic therapy fails: it treats the microbial consequence (SIBO) but not the underlying oxidative driver (iron dysregulation).

3. Physiological Mechanism of Iron-Mediated Neurotoxicity

The core of this hypothesis lies in the biochemical interaction between an accumulated, relatively inert metabolic precursor and an abundance of unchaperoned oxidative iron. I propose a three-step pathophysiological cascade that explains the transition from a latent genetic defect to a severe, multisystemic neurovisceral and oncological syndrome.

3.1. The Genesis of Reactive Iron: HFE and Ceruloplasmin Deficiency

The core of the proposed model lies in the dysregulation of systemic iron homeostasis. Under normal physiological conditions, iron absorption and transport are tightly regulated to prevent the

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presence of free, reactive species. However, in individuals carrying **HFE variants**, even in heterozygosity, there is a recognized tendency toward increased intestinal iron absorption.

The safety of this iron flux depends on its rapid oxidation from the reactive ferrous state (Fe2+) to the stable ferric state (Fe3+)—a process mediated by the ferroxidase activity of **ceruloplasmin**. We hypothesize that when low levels of ceruloplasmin coexist with an HFE-driven increase in iron, the system's buffering capacity is overwhelmed. This may lead to the emergence of **Non-Transferrin-Bound Iron (NTBI)**, specifically in its reactive Fe2+ form, which circulates as a "labile iron pool" capable of triggering oxidative reactions.

3.2. Oxidative Stress and Enteric Dysautonomia

The enteric nervous system (ENS), particularly the unmyelinated neurons of the myenteric plexus, is known to be sensitive to oxidative environments. We suggest that the presence of NTBI facilitates the **Fenton reaction**, where Fe2+ reacts with hydrogen peroxide to generate hydroxyl radicals (·OH).

Rather than causing immediate structural destruction, this chronic oxidative stress may interfere with neuronal signaling and the coordination of the **Migrating Motor Complex (MMC)**. Such an interference would result in gastrointestinal dysmotility and "functional" stasis. This environment may provide the necessary substrate for bacterial overgrowth, explaining why SIBO becomes **refractory**: the bacterial colonization is a secondary consequence of a primary, iron-mediated metabolic interference with autonomic gastrointestinal control.

3.3. Systemic Implications and Inflammatory Context

The potential impact of a pro-oxidative iron pool is not necessarily limited to the gut. Chronic, low-grade oxidative stress is a recognized factor in systemic inflammation. In tissues with high metabolic activity or specific exposure—such as the biliary tract or the cutaneous system—this iron-mediated environment may act as a subtle but persistent stressor.

While a direct causal link to specific oncological processes requires more extensive data, the observation of inflammatory pathologies (e.g., certain lymphomas) in familial clusters with HFE variants suggests that iron dysregulation may contribute to a **pro-inflammatory landscape**. In this framework, managing the systemic iron burden is not just about preventing iron overload, but about mitigating the oxidative "spark" that may drive chronic autonomic and tissue dysfunction.

4. Therapeutic Implications and Management Strategies

4.1. Beyond Antimicrobial Therapy

The refractory nature of SIBO in the context of HFE mutations suggests that repeated cycles of antibiotics (e.g., rifaximin) may only provide temporary symptomatic relief without addressing the underlying cause. If, as hypothesized, the intestinal stasis is driven by iron-mediated oxidative stress on the enteric nervous system, therapeutic priority should shift toward stabilizing iron homeostasis and reducing the production of reactive oxygen species (ROS).

4.2. Therapeutic Phlebotomy as a Primary Intervention

In patients with HFE-mediated iron dysregulation and low ceruloplasmin, even in the absence of clinical hemochromatosis, reducing the systemic iron burden may be beneficial. We propose that **therapeutic phlebotomy** could serve as a definitive strategy to deplete the "labile iron pool" and reduce the levels of **Non-Transferrin-Bound Iron (NTBI)**.

By lowering serum ferritin and normalizing transferrin saturation, phlebotomy may mitigate the oxidative "spark" provided by Fe2+ through the Fenton reaction. This reduction in oxidative pressure could potentially allow for the stabilization or partial recovery of autonomic gastrointestinal function, thereby improving intestinal motility and reducing the recurrence of bacterial overgrowth.

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5. Conclusions

The core of this model is the synergy between **HFE gene variants** and **low ferroxidase activity (ceruloplasmin)**. We conclude that this combination may be sufficient to generate a pool of reactive, non-transferrin-bound iron (NTBI). Through the Fenton reaction, this labile iron could induce a state of chronic, low-grade oxidative interference within the myenteric plexus, leading to the functional stasis that characterizes refractory SIBO.

Clinically, this shift in perspective has implications. It suggests that for a specific subset of patients, the standard cycle of repeated antimicrobial therapy is insufficient because it addresses the microbial consequence rather than the metabolic cause. **Therapeutic phlebotomy** and the rigorous monitoring of iron homeostasis emerge as plausible strategies to reduce the systemic oxidative burden and potentially restore autonomic balance.

Ultimately, moving beyond a purely "functional" or "microbiological" view of SIBO toward a metabolic model centered on iron dysregulation may offer new hope for patients with multisystemic and refractory symptoms. Further clinical research is warranted to validate the efficacy of iron-depletion strategies in preventing long-term autonomic and inflammatory complications in HFE carriers.

References

1. **Brissot, P., Ropert, M., Le Lan, C., & Loréal, O. (2012).** Non-transferrin bound iron: A key role in iron overload and iron toxicity. *Biochimica et Biophysica Acta (BBA)—General Subjects*, 1820(3), 403-410. https://doi.org/10.1016/j.bbagen.2011.07.014
2. **Pietrangelo, A. (2010).** Hereditary hemochromatosis: pathogenesis, diagnosis, and treatment. *Gastroenterology*, 139(2), 393-408. https://doi.org/10.1053/j.gastro.2010.06.013
3. **Pimentel, M., Saad, R. J., Long, M. D., & Rao, S. S. C. (2020).** ACG Clinical Guideline: Small Intestinal Bacterial Overgrowth. *The American Journal of Gastroenterology*, 115(2), 165-178. https://doi.org/10.14309/ajg.0000000000000501
4. **Hellman, N. E., & Gitlin, J. D. (2002).** Ceruloplasmin metabolism and function. *Annual Review of Nutrition*, 22(1), 439-458.
5. **Winterbourn, C. C. (1995).** Toxicity of iron and hydrogen peroxide: the Fenton reaction. *Toxicology Letters*, 82, 969-974. https://doi.org/10.1016/0378-4274(95)03532-X
6. **Torti, S. V., & Torti, F. M. (2013).** Iron and cancer. *Nature Reviews Cancer*, 13(5), 342-355. https://doi.org/10.1038/nrc3508