



H63D Syndrome Research Consortium

www.h63d.org

International H63D Mutation Research Consortium

A non-profit science association. Founded in 2000.

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WARNING

Non-Transferrin-Bound Iron is an overlooked risk factor for iron poisoning and H63D Syndrome Type-1 in patients with chronically elevated transferrin saturation

Scientific letter to the medical community and affected patients!

Non-transferrin-bound iron (NTBI) poses a significant yet under-recognized risk for chronic iron poisoning and the development of H63D Syndrome Type-1 in patients with elevated transferrin saturation. This is primarily due to the limitations of common diagnostic imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT) scans, as well as histopathological staining methods which miss NTBI (more about this below) on a regular basis. The aim of this public letter is to raise awareness among the medical community regarding the importance of early identification and management of patients at risk for chronic iron poisoning and H63D Syndrome Type-1.

We are writing to express our grave concern over a critical yet often overlooked issue in clinical practice: the under-diagnosis of chronic iron poisoning with non-transferrin-bound iron (NTBI) and the associated development of H63D Syndrome Type-1 in patients with a chronically elevated transferrin saturation.

The primary reason for this under-diagnosis lies in the limitations of *all* conventional diagnostic techniques, including histopathological staining and imaging modalities such as magnetic resonance imaging (MRI) and computed tomography (CT) scans.

Non-transferrin-bound iron (NTBI) is not stainable with Prussian blue or any other staining method, leading to false negative results for NTBI accumulation even in most severe cases.



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NTBI is invisible in histopathological examinations and remains without a signal on MRI and CT scans. This leads to a false sense of security regarding a patient's iron status, especially when ferritin levels are within the reference range and no anemia is present. The consequence is an increased risk of chronic iron poisoning and the development of the severe and incurable H63D Syndrome Type-1.

Given the limitations of current diagnostic methods, it is crucial that we identify patients at risk for chronic iron poisoning and H63D Syndrome Type-1 through alternative means. Specifically, patients with medium to rather low (within the reference range) ferritin levels, without anemia, and elevated transferrin saturation should be referred to a specially trained hematologist or endocrinologist for further evaluation.

Appropriate diagnostic testing should include genetic testing for mutations in the HFE gene and other relevant genes. Early identification and management of patients with a predisposition to chronic iron poisoning may significantly reduce the risk of developing H63D Syndrome Type-1, a condition with devastating long-term consequences.

We urge the medical community to recognize the limitations of conventional diagnostic techniques in detecting NTBI and to adopt a much more proactive approach in identifying and managing patients with elevated transferrin saturation. This will undoubtedly improve patient outcomes and minimize the risk of H63D Syndrome Type-1 development.

Remember: wherever you see a significant transferrin saturation (about >50%) chronically, NTBI accumulates in the body.

NTBI, unlike ferritin, cannot be lowered by phlebotomy! You would only further deprive the patient of his/her low ferritin and not remove the NTBI!

Chelation therapies are only an option in cases of acute iron poisoning (e.g. in workers after an industrial accident) due to the disastrous risk-benefit ratio, as they can end lethally if used frequently and repeatedly.

For questions from the scientific community and practicing physicians, we are available for general information at team@h63d.org.

Private individuals may contact us via the contact form on www.h63d.org

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