# H63D-Syndrome: A rare clinical phenotype caused by a homozygous mutation of HFE gene H63D [Short version]

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## Abstract

H63D syndrome is a unique phenotype (clinical picture) of a homozygous mutation of the HFE gene H63D, which is otherwise known to cause at most mild classical hemochromatosis. H63D syndrome is associated with iron overload in the body (especially in the brain, heart, liver, skin and male gonads), but in the form of non-transferrin bound iron (NTBI), not as ferritin. It is an incurable multi-organ disease, leading to permanent disability, which can only be influenced by early diagnosis and a very careful reduction of iron intake (under constant monitoring) as early as in childhood and youth. Our goal was to better highlight the characteristic symptoms of this rare disease to further reduce the risk of missing diagnosing this dangerous condition correctly, even on a primary care level.

## Introduction

Rarely, a homozygous mutation of the HFE gene H63D leads to classical hemochromatosis. Therefore, this mutation is usually considered clinically less relevant than other HFE mutations. However, this is obviously not correct. We report typical symptom constellations in patients with a homozygous mutation of the HFE gene H63D who have developed H63D syndrome. Unlike what is the case in hemochromatosis, the syndrome does not result from ferritin overload but from accumulation of non-transferrin-bound iron (NTBI) due to an unresponsive hypotransferrinemia. The brain, heart, liver, skin and, in males the testes are virtually always affected.

NTBI has the ability to enter numerous cell types and calcium channels. In the cells, it leads to degeneration processes. In advanced stages, therefore, brain damage (especially in the substantia nigra and basal ganglia), cardiac muscle damage or conduction disorders (e.g. heart blocks) may occur. In the cells, NTBI leads to oxidation processes that damage or destroy the affected cells affected and variable dysfunction of the liver are also among the symptoms found in H63D syndrome. The skin shows hyperresponsiveness, and urologists find mildly atrophic testes in affected men.[1-7]

H63D syndrome is an incurable multi-organ disease, leading to permanent disability, which can only be influenced by early diagnosis and a very careful reduction of iron intake (under constant medical monitoring) as early as in childhood and youth. Phlebotomies or dialysis are ineffective in this disease. Bloodletting only causes further loss of vital ferritin. Dialysis does also not lead to a clinically favorable result. The NTBI type iron remains in the cells until they die, only to immediately "move" to a nearby cell. Filtering NTBI from the blood is possible, but due to the described behavior of NTBI, the success would be very limited.[15, 20]

Another factor makes the procedure of dialysis completely useless in H63D syndrome: the basic pathomechanism of the disease is a non-responsive hypotransferrinemia. Since patients with H63D syndrome also need ferritin for survival, a completely iron-free diet is out of the question. Therefore, the "success" of any filtering of NTBI from the blood would be nullified with the next meal. The fact that some physicians nevertheless recommend phlebotomies or filtration therapies can at best be explained by a lack of knowledge. In any case, it is to be warned against it.[2, 5-7]

## Methods

We invited 187 patients with a homozygous H63D gene mutation who have had low non-trigger-responsive transferrin and a chronically elevated transferrin saturation (cut-off value >50%) with normal ferritin and at least two characteristic symptoms of H63D syndrome for further testing. 56 out of 187 (aged 31 to 67, 43 years in average) accepted our invitation to undergo further tests. (The privacy-compliant procedure is described in detail at the end of this study in the "Limitations" paragraph.) These included 3 Tesla contrast enhanced brain MRI, transcranial Doppler sonography, contrast-enhanced ultrasound of the liver, and Doppler ultrasound scans of the heart, kidneys, thyroid, and, in 28 of 31 male patients, testes. Platelet count as well as standard renal and liver function tests were also performed. On top we performed well-established and validated psychiatric and neurologic tests. This allowed us to reevaluate all suspected H63D syndrome cases by detecting typical symptoms of H63D syndrome that might have been missed previously due to lack of knowledge about the existence of H63D syndrome.

**Results**

All patients were found to have a transferrin saturation of 50% or higher. In 72% of the probands, transcranial ultrasound revealed strikingly abnormal findings (striated and roundish whitish lesions) in the area of the substantia nigra. The findings were similar or equal to those that would be expected in patients with Parkinson's disease, however none of the subjects showed shaking palsy.[6,9-11] All MRI scans (3 Tesla) came back negative or inconclusive. However, virtually all patients with abnormal findings on transcranial ultrasonography had some sort of movement disorder, partial or complete loss of sense of smell, and other non-motor symptoms of Parkinson's disease. 42% of those with pathological findings in trancranial sonography suffered from REM sleep disorders and/or narcolepsy, 100% were positive for psychiatric symptoms (mainly OCD like), 96% for further neurological symptoms. Contrast enhanced sonography of the liver revealed signs consistent with a fatty liver of various degree in 74% of the patients (not strictly dependent of the BMI), 39% of the male patients had testicular anomalies (of the regressive type). 64% had moderate eosinophilia, 59% mildly elevated ALAT and/or ASAT values, 82% conduction issues at their hearts and 92% occasionally unpredictable hyper-reactive immune responses mostly affecting the skin. 81% reported chronic constipation with significantly slowed intestinal transit. Most striking was the finding of an average IQ of just 89 in our group of patients. To check the validity of this unexpected result we tested the IQ in a control group of 50 individuals who matched the proband group in all relevant aspects very well. Their average IQ was 103 which makes the value of 89 a significant finding. Further tests (including biopsies) also revealed very clear set of symptoms which is typical for H63D syndrome. Regarding biopsies the pathologists must be aware of the fact that NTBI does not react to Prussian blue which often leads to false-negative liver and skin biopsy for iron.[14-21]

## Discussion

We were able to confirm that the H63D syndrome, as described in medical literature, does indeed have a typical symptom pattern that separates it from hemochromatosis. Patients suffering from H63D syndrome have most of these symptoms:

- Hypotransferrinemia (non-reactive after iron ingestion)
- Chronically elevated transferrin saturation > 50% (multiple testing is recommended due to nutrient-related fluctuations)
- Deposition of NTBI iron in brain and parenchymal tissue
- Slow progressive degeneration of substantia nigra and basal ganglia
- Thought disorders (often highly severe and usually primarily obsessive in nature, compatible with dysfunction of the basal ganglia). Misdiagnosis as a "mental condition" with the consequence of delaying a correct diagnosis is virtually always the case in the early phase
- Tic disorders (variable, often Tourette-like, partly including danger of self-injury)
- REM sleep disorders with risk of self-injury
- Variable motor disorders (in the late course possibly also Parkinson's symptoms)
- Dementia syndromes of various degrees of severity (from mild cognitive impairment to dementia, most compatible with Levy-Body dementia in terms of symptom pattern)
- Drop in IQ measurement results
- Postural instability (idem to Parkinson's disease)

- Narcolepsy, often with cataplexy (if degenerative brain damage has already manifested. In these cases transcranial sonography was 100% positive so that narcolepsy is a marker with the same diagnostic value as a positive transcranial sonography)
- Cardiac damage and cardiac dysfunction (especially conduction defects and arrhythmias)
- Liver damage (even in the early course often an unexplained fatty degeneration of the liver)
- Excessive reactions of the non-adaptive immune system with unpredictable autoimmune reactions
- Disturbed movements in the digestive system (partial paralysis, similar to the issues that are known from Parkinson's syndrome)
- Low to moderate shrinkage of testicular tissue in male patients with degenerative signs on sonography incl. microlithiasis)
- Skin symptoms of variable nature (including impetigo, pruritus, hyperresponsiveness, etc.)
- Mild eosinophilia
- Rare: Renal involvement, ocular disease due to NTBI induced oxidative processes, hearing loss, etc.

## Conclusions

H63D syndrome is indeed a rare phenotype in its own rights of individuals with a homozygenous mutation of their HFE gene H63D. The central pathomechanism is a non-trigger-responsive mild hypotransferrinemia, leading to high transferrin saturation levels with the consequence that iron transforms into non-transferrin bound iron (NTBI) after ingestion. Unlike ferritin or iron bound to other proteins, free NTBI iron cannot be removed from the body. The classical hemochromatosis treatments like phlebotomy etc. are ineffective or even harmful in H63D syndrome, since they remove the "good" and vital ferritin from the patient's body, while the toxic NTBI remains in the cells.

Only a very early diagnosis followed by a medically controlled low-iron diet can slow down the course of the disease in individual cases. Therefore any misinterpretation of the neurologic or psychiatric symptoms as “psychological” with delayed diagnosis of H63D syndrome is a dangerous pitfall which can ruin the health of a young patient irrevocably. In particular, normal values of transferrin saturation should be aimed for, since NTBI normally develops in the human body only at transferrin saturation levels well above 50%.

The usual hemochromatosis treatments can therefore even be extremely dangerous for H63D syndrome patients, since the vital ferritin is normally low in this syndrome and only this is removed from the body during the hemochromatosis treatments. Accordingly, treatment is largely symptom-based with drugs or medical devices. H63D syndrome is still considered incurable, progressive and normally leads to substantial to extreme symptom burden and permanent disability.

## Limitations

To ensure the greatest possible anonymity of the study participants, the necessary tests were arranged by the subjects themselves with physicians of their choice. The data were then transmitted in encoded form. Standards for laboratory tests and medical imaging were set, but the study investigators depended on the integrity of the externally anonymously collected data. Another

limiting factor was the usual interindividual variation among different examining physicians. However, the data reported appear entirely plausible and were also carefully checked in this regard.

## Acknowledgements

We thank all individuals who were willing to volunteer for this study.

## Source of funding and conflicts of interest

No external funding.
No conflicts of interest.

## Ethical standards, compliance, and nature of this scientific work

This article is about the scientific classification of defined medical parameters to identify specific symptom clusters. It is not reporting on a clinical trial (or anything similar), especially not a prospective one. All participating subjects gave informed consent for their inclusion. The study was conducted in accordance with the Declaration of Helsinki. Ethical, data protection, and patient rights requirements of the countries from which data were provided or in which these data were used for research purposes were observed. The examination results of the participating patients were completely anonymized and transmitted to the study personnel with codes that could not be traced. Thus, at no time were personal data generated that could allow conclusions to be drawn about identities.

## Raw data

While this study is in pre-print status, raw data from this study is available upon request.

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