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*Endocrinology*

# Patients suffering from H63D syndrome are at high risk to develop clinically relevant endocrine abnormalities affecting their adrenal glands as well as their HPA and SAM axes

## Abstract

Since H63D syndrome was first described, the authors of this paper systematically investigated for the first time to what extent the adrenal glands, as an integral part of the HPA and SAM axes, are also affected by damage caused by non-transferrin bound iron (NTBI), a hallmark of H63D syndrome. Due to the rarity of the H63D syndrome, the representatives of a number of institutions that regularly deal with the topic in the context of their clinical and research activities have come together for this purpose. Thus, a small but significant amount of patient data could be collected worldwide, analyzed and evaluated, with surprisingly clear pathological results. A secondary aspect is that after reviewing the currently available literature, the team of authors came to the conclusion that the issue of HPA and SAM axes dysfunctions and adrenal synthesis activity seems to be also more frequent in other iron metabolic disorders than it is addressed to in everyday's clinical practice. The result of this work is a warning call to closely monitor the catecholamine balance, the synthesis and control of all "stress hormones", the condition of the adrenal glands as well as other axis structures very early in the course of the H63D syndrome, in order to make unnecessary organ damages at least a little less likely, if not to prevent it to a large extent if detected early.

## H63D Syndrome

Very rarely, a homozygous mutation of the HFE gene H63D leads to classical hereditary hemochromatosis. Therefore, this mutation is usually and wrongly considered clinically less relevant than other HFE mutations. Patients with a homozygous mutation of their HFE gene H63D have an intermediate risk of developing 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 a *static* hypotransferrinemia (almost no reaction to iron intake but an amount enough to keep the individual alive).

The brain, heart, liver, skin and, (in males) the testes are virtually always affected. Ferritin values are often rather low, transferrin saturation most of the time >45% (most commonly 55-95%. NTBI has the ability to enter numerous cell types and calcium as well as sodium channels easily. In the cells, it leads to degeneration processes through ROS triggered micro-inflammation. 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 and quite variable dysfunctions of the liver are also among the symptoms found in H63D syndrome. The skin shows hyper-responsiveness in unforeseeable ways, and urologists will find mildly atrophic testes in affected men (e.g. mostly indirectly like through microlithiasis in sonography).[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 and/or other blood/plasma filtering procedures are ineffective in this disease. Bloodletting only causes further loss of vital ferritin. 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 characteristics 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 has to be warned against it.[2, 5-7]

## Hallmark symptoms of H63D syndrome

**Mandatory for the diagnosis:**

- **Mild to medium hypotransferrinemia** (normally non-reactive after iron ingestion), most commonly caused by a homozygous HFE gene H63D mutation.
- **Chronically elevated transferrin saturation >45% (in most cases 55 to 95%).** Multiple testings are recommended due to nutrient-related fluctuations.

In general, the following symptoms have been in particular typical for H63D syndrome. Not every patient will experience all of these symptoms, though most will, and they are highly variable in severity:

- **Deposition of NTBI iron in the brain, in the heart, the liver and other organs** (using calcium channels and infiltration mechanisms for parenchymal tissue)
- **Slow but progressive degeneration of substantia nigra (SN) and basal ganglia (BG)** Fine damages, first visible in TCS of the SN, later in some high resolution MRI scans. Symptoms indicative for SN and BG damage often years before visible damage (micro-inflammation and iron NTBI deposits).

- **Thought disorders (often highly severe and usually primarily obsessive in nature, compatible with dysfunction of the basal ganglia).** Initially often misdiagnosis as a "mental condition" with the consequence of a dangerously delay of the syndrome.
- **Tic disorders** (very variable, often Tourette-like, partly including danger of self-injury)
- **REM sleep disorders (**with risk of self-injury during sleep)
- **Variable motor disorders** (very variable course)
- **Narcolepsy** with cataplexy
- **Non-motor Parkinson's symptoms**
- **Chronic constipation**
- **Loss of the sense of smell** (sometimes olfactory hallucinations)
- **Dementia-like symptoms of a highly various degrees of severity** (from mild cognitive impairment to full-blown dementia, most compatible with Levy-Body issues and alpha-synucleinopathypies.
- **Drop in IQ** measurement results (~ 45% of the patients
- **Disordered adrenal gland function** (most likely fine structural damages due to infiltration of NTBI into the adrenal cortex, and the medulla
- **HPA and SAM axes regulation** (as a result of damages along structures of the axes, or as a direct consequence of damages to the suprarenal glands)
- **Altered glucose and fat metabolism** (secondary effect due to liver function issues and/or HPA/SAM/adrenal gland damages

## The role of cortisol and adrenaline in H63D syndrome

Over the past five years, the various teams researching H63D syndrome have identified another landmark constellation. It relates to the field of endocrinology. Many patients with clinically relevant H63D syndrome (not just asymptomatic carriers) can suffer quite severely from sequelae in regard to their cortisol metabolism as well as their levels of adrenaline (epinephrine):

A. Due to the direct toxic effect of NTBI.
B. As a result of oxidative cell damage.
C. As a result of destroyed organ structures (often very fine) as a result of micro-inflammatory processes.

Clinicians treating patients with H63D syndrome have noticed in recent years that neuropsychiatric symptoms, together with cryptic abnormalities of liver function that cannot be explained conservatively, are often the first manifest symptoms of H63D syndrome. These may appear as early as childhood and adolescence, whereas cerebral damage tends not to become apparent on imaging until after the age of 30 to 35 years, previously in specific scintigraphies, now mainly in TCS ultrasound. However, the multitude of neuropsychiatric symptoms in H63D syndrome are of such a specific nature that the accumulated data of the past 20 years make a coincidence more than unlikely. Rather, they virtually compel the search for another, fourth level at which H63D syndrome impacts health early in life.

At its Oslo conference, the international H63D consortium therefore called on all physicians clinically familiar with H63D syndrome to perform a structured history and examination protocol in their confirmed H63D syndrome cases (anonymized for the evaluators and after informed consent of the patients). A total of 87 cases aged 17 to 69 years, 40 female, 47 male, mean age 43.7, could be studied.

The results showed overwhelming evidence of pathological values for cortisol and adrenaline in such a way that they did not fit any previously familiar pattern of a known endocrinological disease. However, the collected values of this screening had a highly significantly similar profile in almost all 87 patients, so that in a next step the subjects (after renewed consent, results anonymized) were screened endocrinologically in even greater detail.

The results were of an astonishing similarity even for the expert team:

1. Completely random adrenaline surges (out of the blue).
2. Highly significant excessive adrenaline release in response to known triggers.

3. Prolonged adrenaline release to known triggers (pulsed).
4. Unusually strong and prolonged overlap of adrenaline release and cortisol release.
5. Throttling of the inhibition of the production of ACTH in the sense of a semi-defective "negative feedback" in the dexamethasone suppression test (DST), not on linear nor on exponential up-dosing, but abruptly above a tipping value (highly different between the test subjects, however stable and repeatable).
6. Aldosterone continues to be formed normally via the renin-angiotensin-aldosterone feedback loop.

## APA and SAM axes dysfunctions as well as kynurenine abnormalities in H63D syndrome

Pathologically elevated kynurenine levels could be detected in 127 out of of the 162 patients suffering of H63D syndrome as former studies revealed. The number of patients with an abnormal kynurenine/tryptophan ratio was even higher at 149 out of 162 individuals. A deranged kynurenine/tryptophan ratio is also known from subtle inflammatory processes, various infectious diseases, inflammatory neuropsychiatric conditions, malignant diseases, and it is considered an unspecific but very sensitive indicator of a response to (micro)inflammation on both sides of the blood-brain barrier most commonly caused by the inert immune system. In the context of H63D syndrome, the kynurenine/tryptophan ratio serves clinicians as a relatively reliable surrogate parameter for those crucial as well as subtle inflammatory activity that cannot be detected with standard tests. Especially the chaotic adrenalin-cortisol-regulatory circuits fit well as a physiological correlate to the clinically prominent neuropsychiatric symptoms of the H63D syndrome. The most striking symptoms are uncontrollable and free-floating fears, prolonged panic attacks with a feeling of being ill (exhaustion, cytokine activation), restless flight and fight reflexes ('flight drive', often transformed into exaggerated actions) and most severe compulsive thinking, mimicking psychiatric disorders. As far as possible, we have tried to determine whether these dysfunctions are primarily due to NTBI damage of the adrenal glands or to other pathological processes. Work on this has not yet been completed. However, preliminary raw data and interim results suggest a multifactorial-organic pathogenesis, which would not be an entirely unexpected result of the omnipresence of toxic NTBI iron throughout the organism in H63D syndrome patients.

## Discussion:
## Implications for the treatment of H63D syndrome patients

It can be considered to be highly relevant finding that chaotic patterns of cortisol and adrenalin seem to be not only present in a vast majority of H63D patients. This phenomenon is also the missing biological link that can explain some of the symptoms typical for the syndrome. However, this is very new knowledge and it reliable advice cannot yet be provided on those who are treating this endocrinological component of H63D syndrome. The finding that chaotic cortisol and adrenaline patterns are present in the vast majority of H63D patients has to be considered as highly relevant with far-reaching clinical consequences. This phenomenon was also the missing biological link that now makes some of the syndrome's symptoms easily explainable. However, these are still very recent findings, and it is not yet possible at this time to provide general and/or general therapeutic advice to those clinicians treating this newly discovered and highly problematic endocrinological aspect of H63D syndrome.

However, as a clinician one cannot and should not wait idly until the scientific data suggest a definite treatment approach. The reason: based on what has been known to be true for other conditions, it can be assumed that a stabilization in the sense of a normalization of the HPA and SMA axes, and thus of the adrenal control system, will lead to a decrease of many inflammatory processes in the entire organism, at least to some degree. The links between improperly timed stress

axes and the inert immune system are complex, however, it stands to reason that chaotic pathways with excessive adrenaline and dysregulated cortisol levels negatively affect the proper functioning of the inert immune system without the shadow of a doubt. Last but not least, the pathologic kynurenine regulatory circuit is an indicator, albeit indirect, of this; not to mention the effects of constant adrenaline surges on the brain, heart, and overall metabolism.

## Consequences - steps to take

Numerous complications of the H63D syndrome, especially those of lipid and sugar metabolism, have so far been attributed to the inflammatory direct effect of NTBI. The dysregulation of the adrenal cortex, the medulla and disturbed processes along the SAM and HPA axes with mostly preserved aldosterone balance described in this work can also well explain complications of fat and sugar metabolism. At the present time, the authors of this work assume that both direct oxidative damage (ROS) by NTBI uptake in various organs and pathological performance of adrenal function as well as the associated HPA and SAM axes are capable of exacerbating mutually. A diagnosis of metabolic syndrome in H63D patients with a BMI of <25 to <30 should therefore be made with extreme caution; in no case before an extremely thorough endocrinological workup of the previously described predetermined breaking points. If there are signs of overactivity of the medulla of the adrenal glands or dysfunction of the HPA and SAM axes, however distinct, these should be corrected first before common H63D syndrome symptoms such as nonalcoholic fatty liver disease (NAFLD) due to metabolic syndrome, prediabetes, and similar vogue diagnoses should be made. Premature misattributions in this regard inevitably lead to further reduced quality of life for H63D syndrome patients, increase stress, negative emotions, and drive potential stress hormone dysfunction into a further negative spiral that does not help but harm. Thus, such additional diagnoses can drive especially compliant patients into further rigor to themselves, and at times, further complicate the clinical outcome and quality of life. Therefore, an undogmatic, biological rather than medical interpretation of any endocrinological test results in H63D syndrome patients is to be preferred over standard interpretations based on textbooks which were never written with a condition like H63D syndrome in mind. In the case of very rare diseases it is common mistake to follow guidelines developed for widespread standard diseases - even if the symptoms are similar or sometimes coincide. In any case, it can already be stated that H63D syndrome patients should not be "psychologized" any more than they should be pigeonholed as metabolic syndrome or pre-diabetes patients. H63D syndrome is a condition that lies right at the crossroads of endocrinology, metabolic medicine, gastroenterology, hepatology, hematology, cardiology, urology, neurology, dermatology, immunology, psychiatry, proctology, ophthalmology, radiology, nuclear medicine, and several niche medical fields. Without close coordination between all these specialties, a reasonably successful treatment of H63D syndrome is inconceivable. A highly proactive and communication-oriented attitude by the treating physicians is required as the disciplines are increasingly drifting apart in terms of expertise and organization; and primary care physicians (GPs/ family doctors) are overstrained as a unifying force in the case of such a rare, complex, and dangerous disease.

## Outlook

Therefore, it is obvious to seek the cooperation of experienced endocrinologists in the treatment of the H63D syndrome and to do everything to ensure that unprovoked and/or prolonged adrenaline surges do not persist. In addition, care should be taken to ensure that cortisol is available in sufficient but not excessive amounts in the body. One experimental approach is to inhibit adrenaline synthesis both through central pathways and in the adrenal glands. The only drug capable of doing both simultaneously, and which is as cheap as generally well tolerated (despite its

rather unfortunate image), is alprazolam - most commonly known as Xanax. Under strict medical supervision, the known addictive potential is mostly manageable and the beneficial effects in pathological adrenalin synthesis conditions are extremely promising according to preliminary clinical data.

On the other hand, if the endogenous cortisol release is no longer well regulated due to NTBI-induced damage, it is an obvious option to administer dexamethasone until just above the individual tipping point (see above) and thereby reduce the dysregulated endogenous cortisol production to a minimum without provoking Cushing's disease by overdosing.

An unexpected surrogate parameter for outcome control is the level of blood glucose. It is common for H63D patients to have chaotic blood glucose levels that are not related to malnutrition or even necessarily to type 2 diabetes. This is one of the reasons why the diagnosis of metabolic syndrome is all too often made prematurely in H63D syndrome patients. It is obvious, however, that adrenaline and cortisol excesses can disturb sugar and fat metabolism. If the body's adrenaline synthesis is suppressed and dexamethasone is administered to reach the individual tipping point for a stable cortisol balance in the HPA and SAM axes, the blood glucose metabolism of H63D syndrome patients with a normal BMI usually normalizes as well. This may sound intuitively disturbing at first, but when thought through from the end it is just as logical as it is measurable.

Research on this, especially with regard to long-term effects, is still ongoing. For the time being, therefore, these theoretical therapeutic concepts must be regarded as still unproven and potentially risky. However, the more an endocrinologist is experienced, the more he/she might try such an experimental treatment approach in severely ill H63D patients who are already suffering from organ damage.

## Conflicts of interest

None declared.


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