H63D Syndrome: What we know about it in 2021

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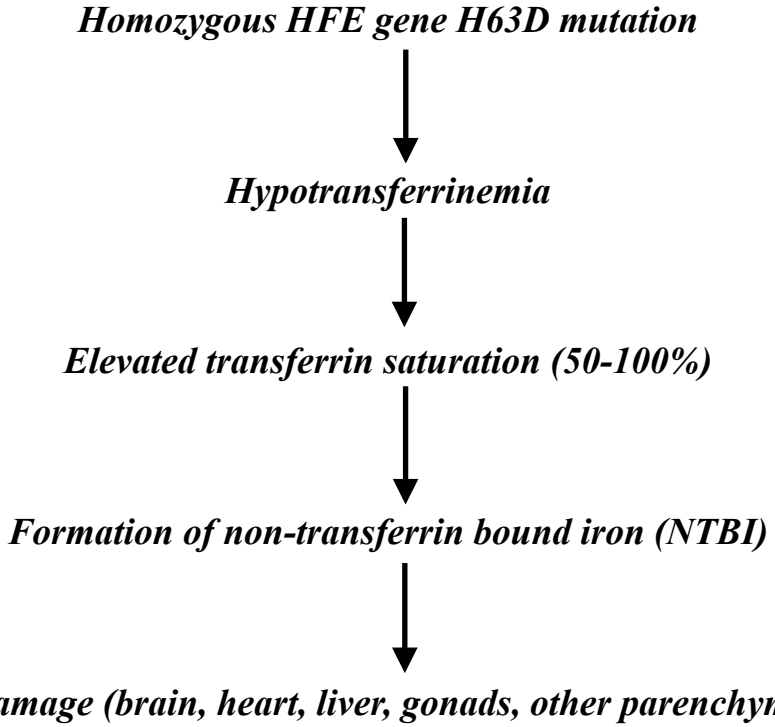
Abstract

H63D syndrome is a serious and clinically progressive disorder of iron metabolism caused by non-transferrin-bound iron (NTBI). In 2019, after scientists from around the world joined together to form the H63D Syndrome Research Consortium (a non-profit entity), a consensus paper "H63D Syndrome" was adopted at a meeting in Oslo in December 2019. With this new paper, we summarize what the leading experts in the field know about the syndrome in 2021.

H63D syndrome

In most practices, clinics and professional societies, a homozygous H63D gene mutation was and is generally considered relatively harmless, since carriers of this mutation very rarely develop classic ferritin-related hemochromatosis. Ferritin levels are usually normal or even rather low in these patients, so everything seems fine. Due to the fragmentation of medicine into many specialties, on a meta-level, hardly anyone has noticed that people with a homozygous H63D mutation can develop a very severe disease, H63D syndrome. The key to understanding the phenotype is non-transferrin-bound iron, or NTBI. H63D syndrome is a separate phenotype (clinical picture) of a homozygous mutation of the HFE gene H63D, which is otherwise known to cause at best a mild classical hemochromatosis. H63D syndrome, however, is not just another type of hemochromatosis, it is a serious syndrome caused by non-transferrin bound iron which is the result of an elevated transferrin saturation (50-100%) due to hypotransferrinemia which is the consequence of a homozygous mutation of HFE gene H63D.[23-25]



The cardinal *difference* between *hemochromatosis* and *H63D syndrome* is the type of iron and its effect on the organs. While classical hemochromatosis causes an overload of ferritin (iron bound to a protein), in H63D syndrome free iron (NTBI) - usually as a result of hypotransferrinemia (too little transferrin) - damages and destroys cells in the brain, heart, liver, skin and (in men) the testes. NTBI has the extreme damaging ability to penetrate certain cell types and calcium channels. It leads to oxidation processes in the cells, which cause severe damage or death of the affected cells.[3,6,28]

In the advanced stages of H63D syndrome, structural brain damage (particularly in the substantia nigra and basal ganglia), heart muscle damage or conduction disorders (e.g. blocks in the ECG) and variable liver dysfunctions are found. The skin shows a hyper-reactivity, urologists sometimes find slightly atrophic testicles in affected men. Liver cells and the skin are also preferred sites of accumulation of NTBI, as in classical hemochromatosis, but NTBI <u>*cannot*</u> be detected in biopsies by staining. NTBI is harmful already in such small amounts that even the MRI technology which is based on magnetic force does not pick up a signal - not even the latest models. This fact has most likely already led to tens of thousands of false diagnoses (*false-negative for iron overload*) and is still an open issue.[20,26,28]

However, H63D syndrome is actually quite easy to diagnose for a trained eye. If a quite young person shows complex neuropsychiatric symptoms (possibly with a hyperechogenicity of the substantia nigra in transcranial ultrasound) as well as a heart condition and abnormalities of the liver and/or testicles together with normal ferritin hypotransferrinemia and a transferrin saturation of >55% (“grey zone” 45%-54%), an HFE genetic test is obligatory. If this shows a homozygous mutation of the HFE gene H63D in the just mentioned constellation of findings, the most likely diagnosis is H63D syndrome.[28,29]

This means NTBI-based iron overload with progressive damage to the corresponding vulnerable organs. If other causes have been conscientiously excluded, the diagnosis in this constellation can be regarded as quite certain. Nevertheless, not every H63D mutation carrier will suffer from exactly the same symptoms. Many remain healthy throughout their lives. This is because the penetrance of the HFE gene mutation H63D is low and means that only a few of the mutation carriers become ill. The next question is what, i.e. which phenotype will develop. In H63D syndrome, damage of the substantia nigra, the basal ganglia, the heart, the liver, etc. is usually seen, although here too with variable symptoms. For example, it is of considerable importance whether there are "only" conduction disorders in the heart (often detectable as blocks in the ECG) or whether, for example, the heart muscle is already damaged. Both are compatible with H63D syndrome and the effect of NTBI on the heart.[6,7,9]

The H63D syndrome, as one of several phenotypes of a homozygous mutation of the HFE gene H63D, is thus diagnosed by means of a synopsis of clinical symptoms and laboratory tests. You might like to use the help of this diagnostic algorithm:

+ Signs of brain dysfunction (including neuropsychiatric symptoms)
+ Heart disease
+ Abnormalities on the liver
+ (Mild) testicular atrophy in men
+ An abnormally high transferrin saturation >50% due to hypotransferrinemia
+ Normal or even very low ferritin
− Exclusion of other causes of disease
+ Positive HFE gene test for a homozygous mutation of H63D
= <u>H63D SYNDROME</u>

The confirmation is obtained genetically by testing the HFE genes for a *homozygous* mutation in the H63D gene in conjunction with a review of the typical clinical features. The mutation as such is not enough to diagnose H63D syndrome. Classical ferritin-hemochromatosis, which is detected in time, is usually well controlled by regular bloodletting. NTBI, on the other hand, cannot be removed from the body in H63D syndrome. Once absorbed, it accumulates and wanders through the organism over the years. There is a certain similarity here to poisoning with other metals, such as copper, lead or aluminum. In Wilson's disease, copper overload occurs, but this is to some extent treatable. The situation is different with other metals. To this class of conditions H63D syndrome belongs and is therefore closer to a chronic metal poisoning than to a storage disease. Of course a patient can suffer from <u>both</u> at the same time, hereditary hemochromatosis (high ferritin) and H63D syndrome (NTBI poisoning).

Since the underlying mechanism is a transferrin deficiency (hypotransferrinemia), in the case of H63D syndrome it can even lead to the paradox situation that the patient has a (too) low ferritin value, but a significantly increased transferrin saturation (TFsat). This means that the normal iron stores are quite empty, the too low iron transporters, on the other hand, are overcrowded and everywhere in the body free NTBI is ravaging in search of cells to penetrate. In brain, heart, liver, skin and testicles it will most likely to be successful. If a doctor now performs a biopsy to rule out hemochromatosis, the cells not “reveal” that they are filled with NTBI because Prussian blue staining does not work at all with NTBI. The test result will be negative, the patient will be classified as "iron healthy", while more and more NTBI will accumulate in the target organs, until gradually the function and/or structure of the affected organs become pathological. Mechanisms other than hypotransferrinemia are possible with a homozygous mutation of H63D according to the relevant literature, but even in these cases, with regard to iron metabolism, TFsat remains the leading criterion, because NTBI can only develop if TFsat is too high.[3,5,18,28]

The usual diagnostic methods of hemochromatosis (ferritin, biopsies with iron staining, MRI) therefore lead in the best case to nothing, in the worst case to a false diagnosis (overlooking the syndrome). The clinical constellation alone, together with a genetic test and the detection of iron and degeneration in the substantia nigra by

means of transcranial ultrasound and tangible findings in the heart and liver and often also in the testicles and skin are decisive. A combination of these factors in the presence of a homozygous mutation of the HFE gene H63D allows the diagnosis.[29]

Progression with typical signs of a synucleinopathy is common as of the 5th decade of life. Recent findings suggest that the onset of narcolepsy with or without cataplexy in the context of H63D syndrome reliably correlates with the appearance of a positive signal on transcranial ultrasonography (white spots and/or streaks, as seen in patients with Parkinson's disease). It is therefore a syndrome that is diagnosed by a defined constellation of findings and not by a single test. A diagnosis made too late is a major problem in many storage diseases.[5,6,8,12,29]

Not less striking is the recent observation that the severity of tics decreases as the symptoms of narcolepsy with cataplexy become more severe. To date, we do not have a definitive explanation for this phenomenon; however, it is not far-fetched to conclude that a progressive pattern of destruction in the basal ganglia and adjacent areas may lead to a shift in symptoms.

At about the same stage, cognitive deficits become noticeable, initially more as concentration issues and/or intelligence reduction (drop in IQ) than as forgetfulness. The latter might gradually appear at a later stage. The reason is usually that the accumulation of the stored substance follows a linear pattern, and symptoms in many cases begin to creep in just as gradually. Particularly in long-standing doctor-patient relationships, it is therefore not uncommon that a fresh look is missing and the person suffering from the disease is already in a box from which it is difficult to break out, for the practitioner as well as for the patient.[24,29]

However, common sense often helps. If, for example, a young woman shows an increasing number of strange disorders of the vulnerable organs or if a key indicator value, metaphorically speaking, (suddenly) flickers up on the laboratory sheet for no good reason; then one should get rid of the idea that the rare is rare and arrange for further diagnostics. Rare diseases are indeed rare and frequent ones are frequent. However, rare does not mean "non-existent".

The rare also exists. Unlike ferritin or iron bound to other proteins, free NTBI iron cannot be removed from the body as a regular therapy. The classic hemochromatosis treatments by means of bloodletting etc. are ineffective or even harmful in the case of H63D syndrome, as they remove the "good" and vital ferritin from the patient's body (of which he/she has often barely enough) while mainly the toxic NTBI remains in the organism; and even if NTBI gets removed to some extent it will be back with the next meals. Only an early diagnosis followed by a physician-controlled low-iron diet can slow down the course of the disease in some cases if caught in the first or second decade of life.[12,26]

In any case, hidden sources of iron should be strictly avoided, for example in breakfast cereals, vegan meat substitutes (especially when containing soy-protein concentrates), multivitamin preparations and the like. The patient should also be informed that even a well-adjusted diet will not protect him or her from phases with high TFsat levels. The cells of the human organism do not always renew themselves to the same extent, so there may be periods during which increased cell renewal occurs, with the release of NTBI and higher TFsat as a result.[12]

A sudden increase in TFsat in the blood under correct diet is therefore possible and is not necessarily an indication of the failure of a low-iron diet. The success of illness management in H63D syndrome is determined by a well-coordinated communication between all the doctors treating a patient. Structural damage that has already occurred (e.g. degeneration of the brain) cannot be reversed. Nevertheless, a dietary limited iron intake can in individual cases slow down the progression of the disease and reduce purely functional symptoms to a certain extent.[29]

However, miracles should not be hoped for. Patients with pronounced cataplexies should be equipped with appropriate protection, ranging from medical safety helmets to orthoses and wheelchairs to prevent cataplexy-related injuries. Sometimes the patients need supportive social counseling to learn to accept their medical aids. For those who need a wheelchair training in a rehabilitation center has shown some promising results. Many patients show a profound lack of compliance in this regard. However, compliance should be ensured, as H63D syndrome patients with cataplexies regularly underestimate their risk of injury. Nevertheless, there is currently no better therapy option than a correct diagnosis very early in life, a medically supervised reduction of iron intake and the protection of the patients from further harm.[24]

It is high time that the existence of the H63D syndrome reaches the mind of every medical professional around the world. Especially where all the wires come together: at the family doctors, or general practitioners. Human fates depend on it. No pharmaceutical company or professional association has a vested interest in making the H63D syndrome and its consequences better known. Because relatively few people suffer from it, but above all, no money can be made from it.

It would certainly be possible for an innovation-driven company to develop a drug that prevents the formation of NTBI in the organism or that would easily replace missing transferrin. But the market is simply too small for such an expensive venture. Therefore, not much can be expected from this direction. People suffering from H63D syndrome (NTBI caused iron overload due to a chronic hypotransferrinemia) and their relatives must become their own experts and remind the treating physicians again and again to keep an eye on the bigger picture.[10-14]

Cardinal symptoms

- Variable motor disturbances, in the late course possibly also Parkinson's symptoms.
- Typical symptoms of synucleinopathies.
- Narcolepsy, often with cataplexy - when manifestation of degenerative and irreversible brain damage has already occurred.
- Thought disorders: Often highly severe and usually primarily obsessive in nature, compatible with dysfunction of the basal ganglia. They are often misdiagnosed as "mental illness", especially in the early phase of the disease. If thought disorders are in the foreground, a correct diagnosis is therefore often delayed.
- Tic disorders: variable Tourette's-like tics and hyperkinesis, sometimes with a risk of self-injury.
- REM sleep disorder with risk of self-injury.
- Postural instability.
- Dementia syndromes of varying severity from mild cognitive impairment to full-blown dementia, consistent with signs of synucleinopathy.
- Progressive limitations in general cognitive performance, including partial variants.
- Decline of the intelligence quotient despite preserved selective performance in diagnostically relatively well definable areas. Often the linguistic intelligence remains normal for a long time, so that the mental decline is not noticed by the social environment at first (usually until the fourth and fifth decade of life). These slowly progressive symptoms usually precede a comprehensive dementia development in the narrower sense. However, they are not to be understood as a prodromal stage, but as an independent symptom complex that does not always have complete dementia as its endpoint.
- Cardiac damage and cardiac dysfunction, especially conduction defects and arrhythmias
- Liver damage (even early in the course, often an unexplained steatosis)
- Excessive episodes of the inert part of the immune system with highly variable autoimmune reactions, including periods of decreased defense of the adaptive immune system.
- Fibrosis of various organ systems, including skin.
- Disturbed motility in the digestive system, usually constipation, less frequently also bloating.
- Testicular atrophy in male patients, sometimes with degenerative signs on sonography
- Skin symptoms of variable nature (including impetigo, pruritus, hyper-reactivity, etc.)
- Rare: Renal involvement, ocular disease due to NTBI-induced oxidative processes, hearing loss, chronic eosinophilia with possible structural damage to the heart.

Summary

- HFE gene H63D mutation and the H63D syndrome are not the same. One has to use precise language in communication to avoid unnecessary confusion.
- The H63D gene mutation can rarely cause classical hemochromatosis. Either as a homozygous mutation or heterozygous together with another heterozygous mutated HFE gene
- The HFE gene H63D mutation can cause H63D syndrome. This usually only affects people with a homozygous mutation of this gene
- In case of H63D syndrome, ferritin levels are normal or even very low. Hypotransferrinemia is also often present, but there is always an excessively high transferrin saturation (>50% and more on average).
- In H63D syndrome, labile iron in the form of NTBI accumulates in the above-mentioned organs and leads to dysfunctions and/or organ damage.
- Ferritin can be detected by MRI and biopsy, NTBI iron and H63D syndrome is not detectable with these methods.
- A transcranial sonography can detect different types of iron in the brain.
- The onset of severe narcolepsy with cataplexy can be use as a substitute marker for transcranial sonography, especially in less well equipped countries, since we found a very strong correlation between the onset of narcolepsy with cataplexy and white abnormalities in the transcranial sonography of H63D syndrome patients.
- As soon as the above mentioned changes appear in the substantia nigra and part of the basal ganglia the illness enters the phase of synucleinopathy.
- Many doctors, unlike scientists, do not know about H63D syndrome. This has its cause in the rarity of the disease.
- Not all people with H63D syndrome have exactly the same symptoms. Most often, however, the brain, heart, liver, skin and testicles are affected.
- H63D syndrome can affect women as well as men of all heritages.
- Phlebotomy and chelation therapies are contraindicated in pure H63D syndrome because, among other things, the levels of ferritin in these patients are (too) low anyway and NTBI cannot be filtered out of the body constantly.
- Some H63D patients experience a first episode in their early youth with a foudroyant (flash like) onset of symptoms, usually after an infectious disease. It is not yet known why this is the case in some people with H63D syndrome.
- Your doctor may not know about H63D syndrome yet. Show him this information and make sure to emphasize that it is about NTBI (a special form of free iron) overload.

Conflicts of interest

None.

Ethical standards and patient's rights

This paper is in accordance with the Declaration of Helsinki.

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