Stronger together

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HFE H63D mutation: why are you killing your patients?

ABSTRACT

Evidence-based medicine has shown for many years that homozygous mutations of the HFE gene H63D are by no means negligible. Not only can it cause, usually after a second hit, rather mild classical hemochromatosis, but it can also cause numerous other disorders of iron metabolism, such as hypotransferrinemia, changes in binding capacity, and others. In addition, it may lead - among other symptoms - to damages of the heart and the substantia nigra via a causal relationship that remains to be investigated, most likely via a cascade dysfunction in iron metabolism. The clinical facts are compelling. Any physician who dismisses mutations of the HFE gene H63D as clinically irrelevant risks the health and life of his patient. We report two patients with an HFE H63D mutation who were treated almost too decades too late because of outdated expertise.

INTRODUCTION

Homozygous mutations of the HFE gene H63D have not been taken seriously enough for many decades. This mutation of gene H63D is a Pandora's box. It has been linked to liver disease, bone and joint disease, diabetes mellitus, heart disease, hormonal disorders, porphyria cutanea tarda (PCT), infertility, stroke, severe neurodegenerative disease, cancer, venous peripheral artery disease, hereditary hemochromatosis (after a second hit), and H63D syndrome. In the years since the discovery of HFE and its mutations, researchers have focused their studies primarily on the C282Y mutation because it is particularly common in people with elevated iron levels. About 85% of people with abnormally high iron levels have two copies of C282Y, so this mutation has been studied more intensively. Other mutations, such as S65C or H63D, have not attracted the attention of researchers. The S65C mutation can lead to mild to moderate hepatic (liver) iron overload, especially in combination with other mutations. Increased serum iron indices and iron overload have been observed in C282Y/ S65C compound heterozygotes. In scientific evaluation, H63D stands out as a significant modifier of disease onset, disease progression and even

response to therapy. H63D is associated with arterial rigidity, prooxidation, higher total and low-density lipoprotein cholesterol, acute lymphoblastic leukemia (ALL), decreased sperm production, and higher risk of type II diabetes mellitus, and hereditary hemochromatosis after a second hit. Being a carrier of the H63D hemochromatosis mutation is also a risk factor for earlier onset and longer duration of kidney disease in type II diabetics. The most striking risk associated with H63D is that for neurodegenerative disease. Connor and colleagues were among the first researchers to examine the role of H63D in brain iron accumulation, oxidative stress, and neurotransmitter performance. Connor reported that the HFE variant H63D contributes to many of the processes associated with various types of dementia. These processes include increased cellular iron, oxidative stress (free radical activity), glutamate dyshomeostasis (abnormal balance), and an increase in tau phosphorylation (abnormal levels of tau proteins can lead to dementias such as Alzheimer's disease). As demonstrated by Jacobs, Papadopoulos Kaufmann, and colleagues (2012, 2015, 2017, 2019, 2020, 2021) using solid patient data, the numerous damages in parenchymal tissues, heart, and brain (substantia nigra and basal ganglia) can be explained by insidious non-transferrin-bound iron (NTBI) intoxication as a consequence of chronic transferrin saturation of >50%. This constellation (H63D syndrome) is similar to Wilson's disease, except that NTBI iron, rather than copper, is the culprit here. In addition, the damage caused by H63D syndrome is more widespread in the body, affecting not only the liver but also the heart, brain, and in men, the testes. Synucleinopathies are a major problem of H63D syndrome, but other forms of cognitive decline are also common. Connor states further that HFE H63D cells have been shown to have more oxidative stress, further supporting their role as modifiers of neurodegenerative diseases. He found that patients homozygous for H63D had earlier signs of mild cognitive impairment and earlier onset of dementia disease than patients with normal HFE H63D or H63D heterozygote individuals. Despite this fact, which has been known for 25 years, many clinicians still dismiss homozygous HFE-H63D mutations as irrelevant. Even some of the highest authorities in the field of iron metabolism seem to be trapped in the knowledge of the early 1990s.[1-17]

CASES

Patient 1

Male, 46 years, Southern European, with Parkinson's-like neurological symptoms, incipient dementia, loss of IQ by >40%, steatosis hepatis, regressed testes, cryptic (mainly vesicular) skin lesions, mildly impaired lipid metabolism (with a BMI of 22), and high-grade cardiac conduction abnormalities due to micro-scarring. The patient was unsuccessfully investigated by all means of modern medicine from 1997 to 2018, without any of the total >70 colleagues involved taking the patient’s most severely disturbed iron metabolism seriously. The patient's ferritin has always been at the lower range of the norm, while his transferrin is statically 20% below the norm, no matter which laboratory or method is used. As a result, transferrin saturation (TFsat) values of 60-90% are the result. Postpradnial no transferrin response, the level of this crucial iron transporter remains static. Due to the consequence, high TFsat values, it must be taken for granted that there is a constant release of NTBI in his organism. All other proteins, etc. are normal. Albumin is high-normal. We interpret this as a reactive attempt by the patient’s body to compensate for the lack of transferrin, especially postpradnial. In biopsies, no Prussian blue reaction, which was to be expected given his low ferritin and non-stainable NTBI. On skin biopsy, a histopathologist thought he saw what was considered iron in the dermal and sub-dermal layers. We found the patient’s substantia nigra full of iron and scars (white in TCS), he has been suffering from non-motor Parkinsonism, movement disorders, tics, most severe narcolepsy with cataplexy, early signs of dementia, and REM sleep disorders. He also suffers from left bundle branch block (LBBB) due to micro-scarring with decreasing left ventricular ejection fraction (Teichhaus method). Sudden episodes of immune system overdrive are observed, resulting in small bullous skin and mucosal symptoms, petechiae, and leaking capillaries (with normal platelet count and other normal test parameters), as well as skin disorders that seasoned dermatologists refer to as "autoimmune" or "toxic." Steatosis hepatis at a BMI of 23, regressive hyperplasia nodule in the liver with an abundance of calcifications, testicular parenchyma regressive with progressive calcifications (bilateral). Basophilia, eosinophilia, slightly low MCH, MCV with normal Hb. Chelation therapy was not tried due to very low ferritin levels. Administration of transferrin by plasma infusion was discussed but dismissed because of the often overshooting immune responses seen in this

patient; especially since the effect of constant plasma therapy is questionable in the presence of already manifest organ damage. A medically supervised low iron diet showed a drop in TFsat by one third with borderline low ferritin. If the high TFsat values had been considered clinically relevant before the organ damages manifested and the mutation of the HFE gene H63D had not been downplayed, the patient would be, most likely, in a much better clinical condition today. Instead, one organ after the other has been damaged. A low-iron diet currently remains the only causal treatment option in this patient, and the medium- and long-term prognosis is unforeseeable.

Patient 2

Male, 44 years, Western European. Latest since 2005 highly significant elevated ferritin levels with strikingly low transferrin values. The transferrin level is within normal range but insufficiently reactive. No treatment offered by any physician consulted in the United States and Europe for 16 years. In his mid-30s development of metabolic syndrome with hepatic steatosis and short after manifestation of type 2 diabetes. Still no reaction to the abnormal iron metabolism by all treating physicians. Instead, the patient was made responsible for his manyfold symptoms due to his moderately elevated BMI. This is nothing but malpractice and victim blaming in a clinical setting. Still no treatment for his highly elevated ferritin for nine more years. Eventually detection of a homozygous HFE gene H63D mutation with the awareness of a endocrinologist and a practice for rare diseases. To date, no other mutations have been detectable. The patient will now be treated for hemochromatosis with abnormally reacting transferrin. One of the leading ‘iron experts’ in western Europe who ignored the highly abnormal ferritin and only partly reactive transferrin already before is still opposing treatment because one should “disregard the HFE H63D variant which has been well described as non deleterious”. Basically, this statement is nothing less than a call for negligent homicide.

DISCUSSION

As physicians specialized in rare diseases, we regularly see patients with complex syndromes consistent with those mentioned before. Just as regularly homozygous mutations of HFE gene H63D are found as primum movens (primary cause) of complex metabolic and toxic syndromes. It is also typical for treating colleagues to ignore this finding, as old textbooks (and new ones copy-pasted from old ones) still state that the HFE gene H63D or its homozygous mutation would be clinically irrelevant.

This is false, misleading and potentially deadly misinformation.

The knowledge about the high clinical relevance is neither new nor a fringe topic. HFE H63D is not a strong hemochromatosis gene, however, with a second hit it can easily cause hereditary hemochromatosis. But even more important than this, a homozygous mutation of the HFE gene H63D is, according to overwhelming evidence, responsible for many cases of complex syndromes associated with heterogeneously altered iron metabolism.[1-68]

- Patient 1 has a type of "Iron Morbus Wilson," correctly referred to as “H63D syndrome”, due to a persistent NTBI production in his organism. Treatment is mainly symptomatic, causal by a low iron diet under medical supervision. The prognosis is unclear.
- Patient 2, most likely due to a secondary hit (presumably his increased BMI), has developed hemochromatosis with further disturbances in his metabolism. This is due to the homozygous mutation of his HFE gene H63D. No other reason was found, not even remotely. His diabetes mellitus may very well be a consequence of his iron overload, a fact that has been obscured and ignored because of the stigmatization and discrimination against moderately obese patients. His prognosis is slightly better than that of patient 1, as classical hemochromatosis treatment may slow the progression of sequelae in him.

CONCLUSION

Both patients stand as pars pro toto. They are not exceptions but two typical representatives of a considerable patient collective. The correct assessment of the clinical relevance of a homozygous mutation of the gene HFE H63D with its heterogeneous clinical picture must finally be taken most seriously also outside the realm of medical research.

Otherwise, we as clinicians will continue to kill our patients based on outdated "knowledge", even though all recent findings on the HFE gene H63D are freely available to everyone.

CONFLICTS OF INTEREST

None declared.

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