



## H63D Syndrome Research Consortium

# H63D Syndrome: data and facts

*Note to the scientific community*

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### Jacob S. Adams, PhD

## Co-founder of the H63D Research Consortium

Ever since I co-founded the International H63D Research Consortium, I have always considered it my duty to pass on the most important knowledge about H63D syndrome to my colleagues in academia, research and applied medicine. Before I leave the consortium for a new career step, there are still some data to be published, which my current colleagues will certainly work on in more detail at a later stage. After all, knowledge can save lives and prevent suffering. I will publish these data in the following, because they speak for themselves.

\*Dr. Diamandis contributed as an assistant to Dr. Jacobs

## Introduction

### Striking findings in H63D syndrome patients

Caused by a homozygous mutation of the HFE gene H63D leading to a chain of dysfunctions (non-responsive hypotransferrinemia -> transferrin saturation 50% or higher -> NTBI "non-transferrin bound iron" poisoning -> H63D syndrome), still very little to nothing is known about the multifaceted symptomatology of this severe disease by frontline physicians. This despite the fact that it is not difficult to recognize the symptom if the patient is seen as a whole and not only from the point of view of one's own specialty. So you will hardly find a H63D syndrome patient without severe tics and/or cognitive decline and/or REM sleep disorders and/or narcolepsy with cataplexy and/or cardiac damage and/or liver dysfunction and not infrequently even damage to the male gonads. Transcranial sonography often shows a Parkinson's-like pattern from the 5th decade of life. As we have shown in previous studies, narcolepsy with cataplexy is a cardinal symptom of advanced H63D syndrome that correlates with findings consistent with brain damage on transcranial sonography (hyper-echogenicity in the substantia nigra and abnormal findings in parts of the basal ganglia), as shown in Figure 1 below.<sup>14-18</sup>



Fig.1 (TCS)      Substantia nigra echogenicity  
(normal) in a healthy individual



Substantia nigra hyper-echogenicity  
as found in H63D syndrome

To investigate as many aspects of this under-researched disease as possible, we used data from external research groups after 2019. Overall, the data were good, in some cases excellent. I will now focus only on the excellent data. To do this, we collaborated with Western-standard clinics in the Middle East, Africa, and India affiliated with the International H63D Syndrome Research Consortium. The results were provided to us in a fully anonymized form. As an unexpected finding, we became aware of an inverse correlation of motor symptoms and narcolepsy with cataplexy in direct correlation with transcranial sonography (TCS) findings of the above type (Fig. 1) But there is more.<sup>17,18</sup>

## Method and TCS-scan findings

Two hundred patients with relevant cataplexy seizures, defined as more than 2 seizures with falls and/or injuries and/or property damage, aged 24 to 49 years, mean age 32 (169 male, 31 female, no significant sex difference in results) were interviewed with structured questionnaires about their symptoms, disease course, and other aspects of their condition; and each of them had at least one transcranial sonography with modern equipment and physicians who were very well trained in this very specific type of ultrasound procedure. We asked the sonography experts to provide, in addition to their normal reports, a severity scale ranging from zero (normal substantia nigra) to (very hyper-echogenic substantia nigra). The average was 6.8 points, up 1.8 points in patients younger than 40, and 9.1 points in those older than 55.

## Tic to narcolepsy shift

To our own surprise, in this data we found a striking and robust pattern consistent with the anecdotal description of disease progression as reported by the patients themselves. It seems that the progressive destruction of the substantia nigra and neighboring areas of the brain leads to reduction in tic severity and the development to narcolepsy with cataplexy, or even narcolepsy and cataplexy as independent symptoms.

### Tics vs. Narcolepsy/Cataplexy in H63D patients

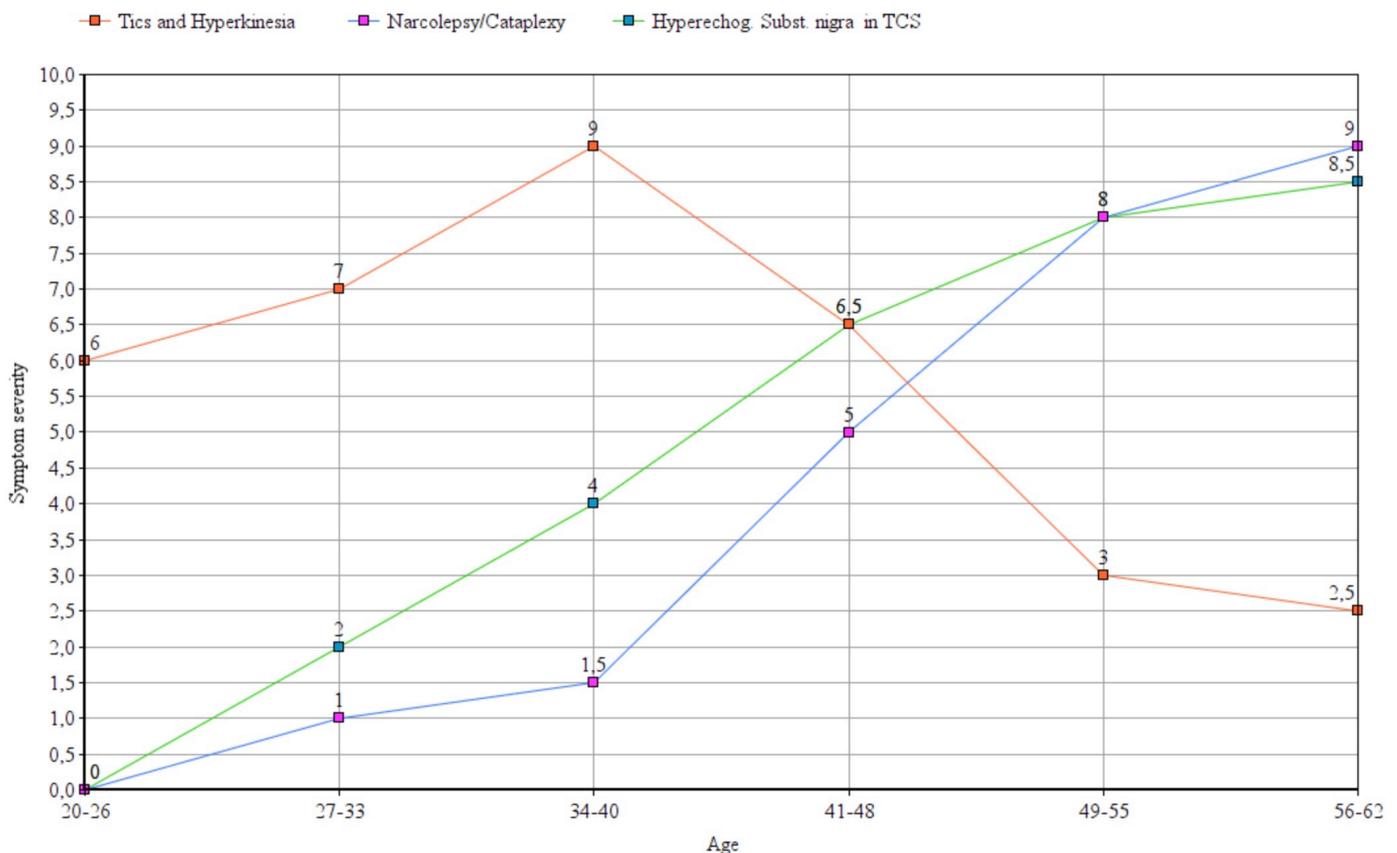


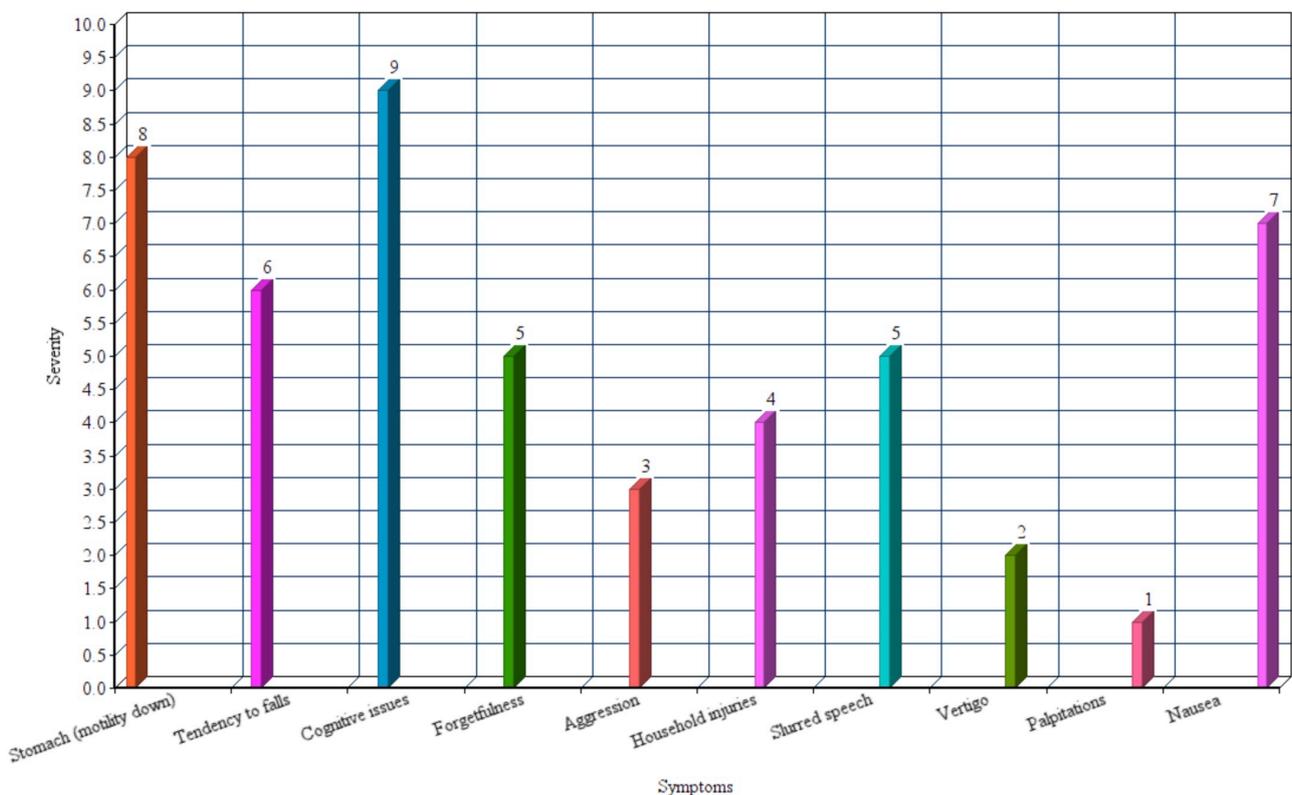
Fig. 2

As can be seen well in this pooled graph, there seems to be a strong inverse correlation between certain motor symptoms (e.g., tics, hyperkinesia) and severe narcolepsy with cataplexy. The differences between male and female patients are not significant. The results of transcranial sonography (TCS) were even more striking. Progressive damage to the substantia nigra appears to correlate with the sharp increase in symptom severity of narcolepsy with cataplexy (or one of these symptoms alone) in patients with H63D syndrome, with tics decreasing the more substantia nigra damage becomes visible in TCS. To date, we have different hypotheses but no satisfactory explanation for this finding.

## Dysfunctions due to inhibited narcolepsy attacks

In narcolepsy with cataplexy as a symptom of H63D syndrome, we noticed a phenomenon that has not yet been described by any other scientist or group of researchers. Whenever subjects succeeded in inhibiting an incipient seizure and did not fall asleep, they developed other symptoms that appear to the observer as "sleep-related partial inhibition or reduction of body functions while being awake." This is a broad area for future research, as it may even help explain comorbidities in primary narcolepsy.

Dysfunctions when narcolepsy attacks are being inhibited

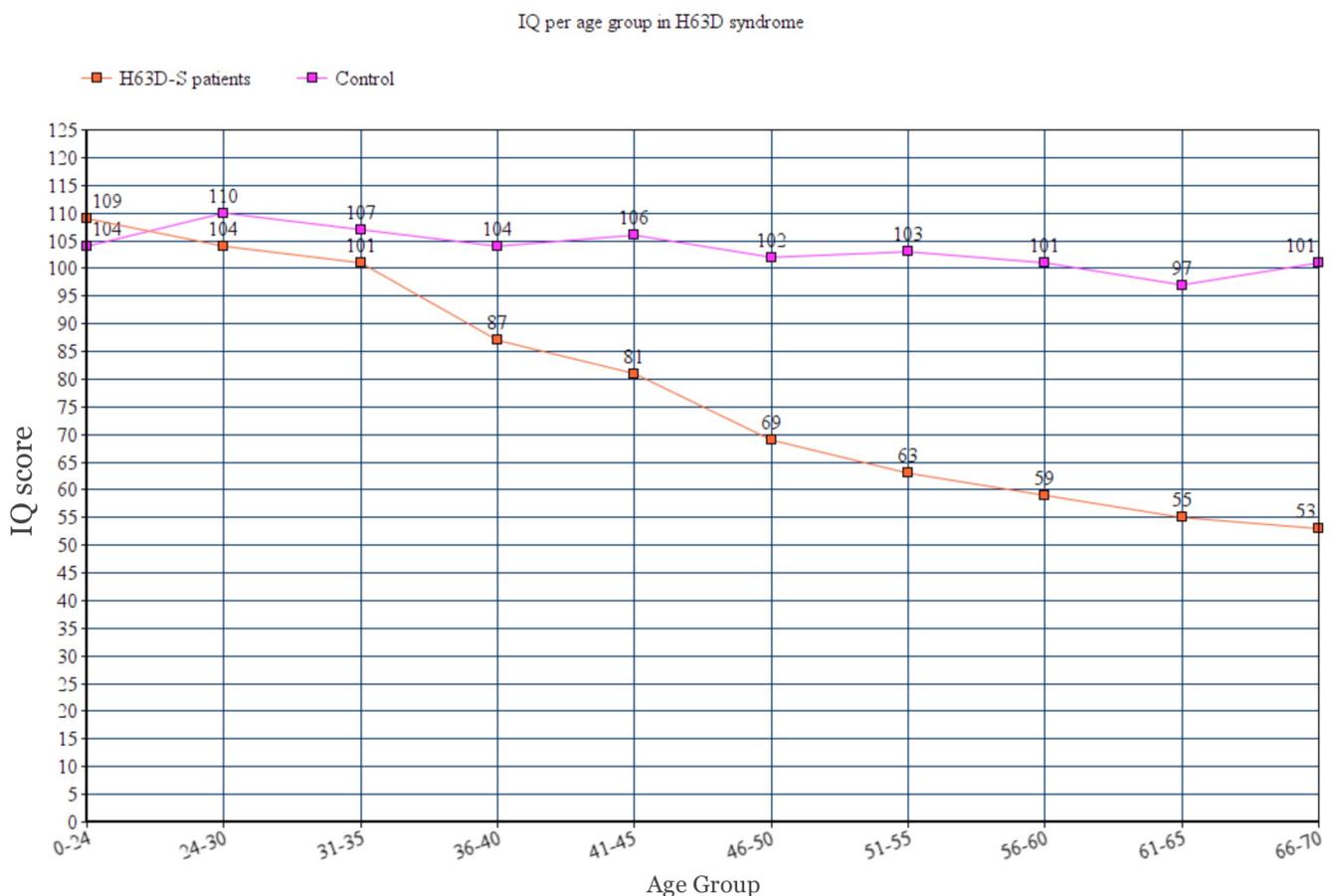


There are more symptoms to be found in this very unique phenomenon after attack inhibition. In order to not overwhelm the reader we focused here on the most important ones.

Interestingly, the reduced function of gastric motility in particular could be part of the explanation why narcoleptics tend to be overweight.<sup>55</sup> On the one hand, during inhibited attacks there is still food in their stomach from meals taken hours ago and, at the same time, the lower digestive system sends signals to the brain that it is time to eat again. Thus, even during and shortly after a narcoleptic seizure, we see slightly elevated serum glucose levels, even if the seizures have been inhibited and the patient has remained awake. These values suddenly drop again once gastric motility returns to normal.

## IQ decline in H63D syndrome

A significant number of patients with H63D syndrome develops dementia, most likely due to synucleinopathy. Independent of this issue, a significant drop in IQ can be observed in more than 72% of patients compared to corresponding control groups. To date, we do not have a satisfactory explanation for this aspect, which is probably still substantially underestimated because the effects are less noticeable in everyday life when compared to dementia. Nevertheless, a linear 50% decrease in professionally measured IQ, as shown in the table below, is not only highly significant but also concerning. Considering that most patients have a profession with certain responsibilities, a significant decline in IQ is a matter of public safety. In this case, physicians must not look away simply because IQ loss is a difficult matter to communicate. As the signs are more subtle than those of dementia, families and caregivers must also learn to recognize the signs and symptoms of IQ loss. One very common early sign is a rise in accidental writing errors, may they be misspelling or using associated words like “wood” instead of “tree”.

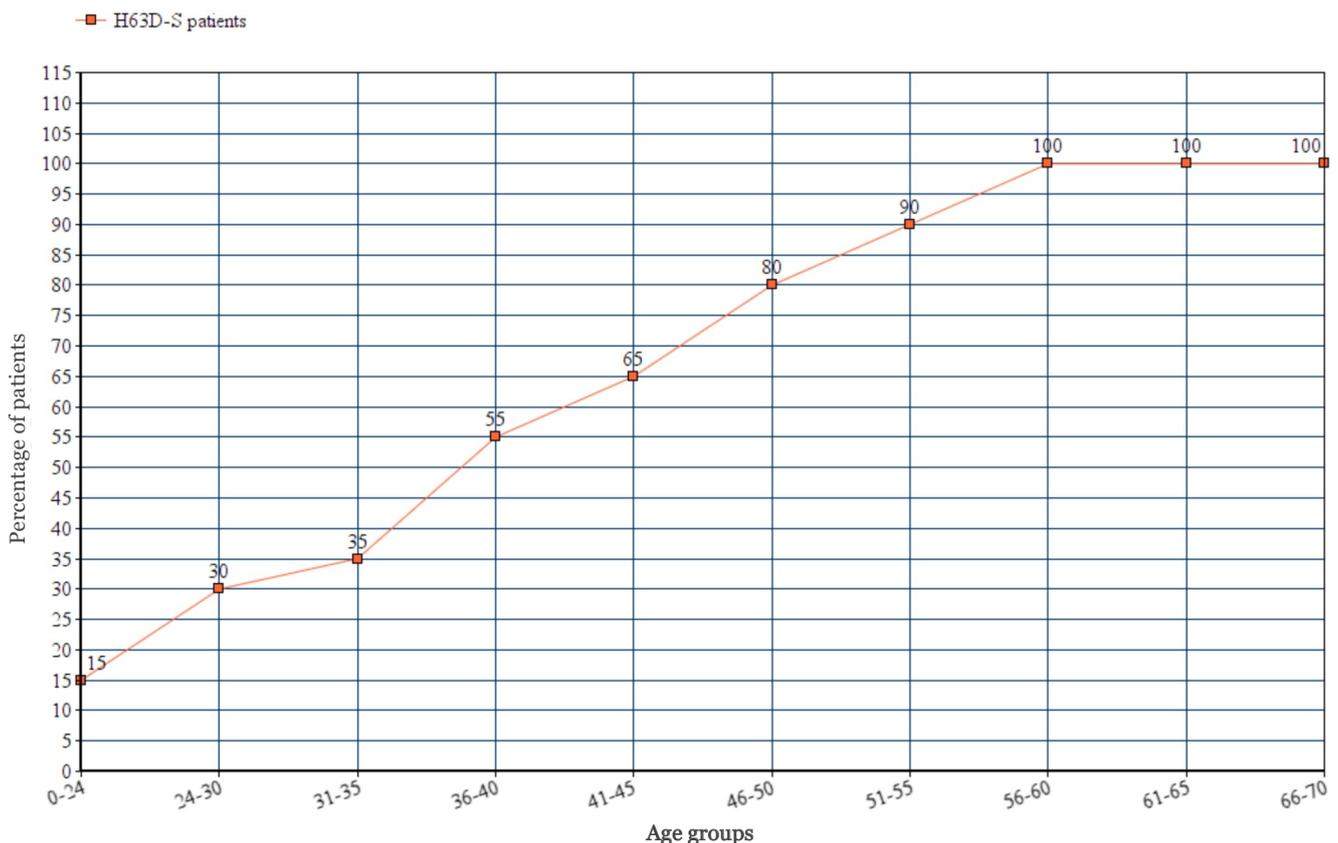


In most cases, the diagnosis is still made too late, which leads to dangerous work errors, failures in the household, problems keeping up intellectually with peers and the danger of overestimating one's own abilities. Since science and medicine have yet to answer the question of which of the brain damages due to NTBI causes this brain symptom in H63D syndrome, let alone how to treat this IQ loss, counseling is usually helpful in learning to live with this progressive limitation. Interestingly, the issue of memory impairment does not seem to match in any way with this loss of brain power we see in patients with H63D syndrome. Our patients can remember but not use their knowledge as they could in the past. It's like they know exactly what a puzzle is and how it should work, but they are not able anymore to use this knowledge in a practical way. So, a businessman with an IQ of 65 at age 47 is not as mentally capable as he was with an IQ of 109 when he graduated from college, even without losing his memory. Because he has no memory loss and since he can still remember things quite well, most people around him will not notice his sharp cognitive decline until he makes a big mistake. Therefore, depending on the profession, it should not be a taboo to make these patients leave their jobs (retire) if their IQ has dropped by 25% within 15 years or if their IQ falls below a cut-off range of 75-90, depending on their job.

## Severe disability due to H63D syndrome

Based on data from different countries with different ways to define the impairment of an individual we transferred these values into a percent scheme from 0% to 115%. The latter is due to some countries adding disability values while others have an inclusive model.

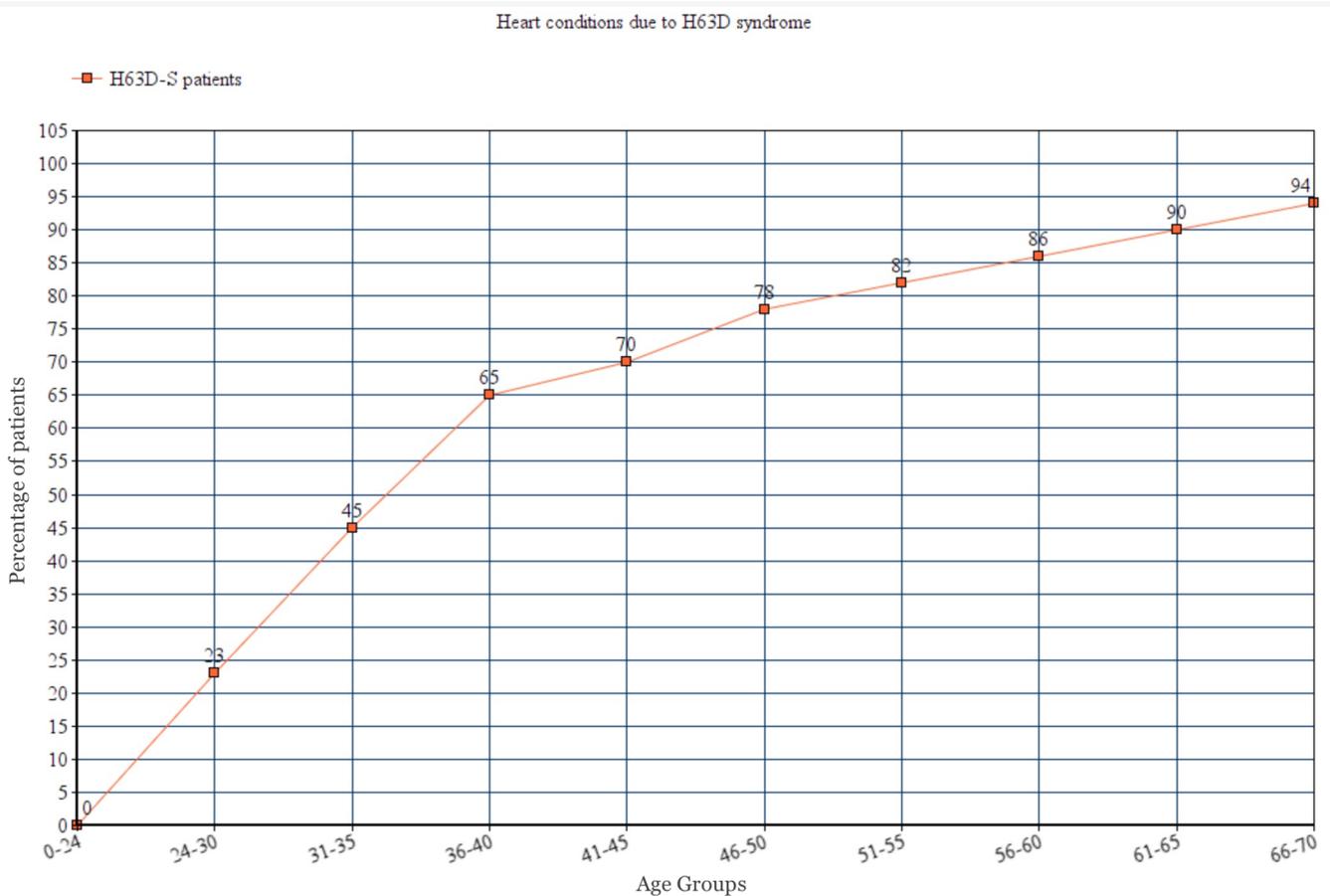
Disability in % according to S A DSC



## Heart conditions due to H63D syndrome

Cardiac problems are common in H63D syndrome, however, they can be of diverse etiology. Chronically elevated eosinophils, palpitation, calcium channel dysfunction, fibrosis, conduction disturbances (heart blocks) - all of these can occur at high NTBI levels (the basis of the pathomechanism) and cause transient to permanent damage.<sup>53</sup>

Despite transient symptoms may occur, the prevalence correlates positively with age. With H63D being sort if a chronic NTBI poisoning this correlation makes sense. as well has the fact that younger H63D syndrome often report about palpitations rather early in life. This leads to the hypotheses that NTBI in lower doses might cause "harmless" functional issues while an accumulation of more NTBI during many years might lead to more severe structural damage.<sup>54</sup>



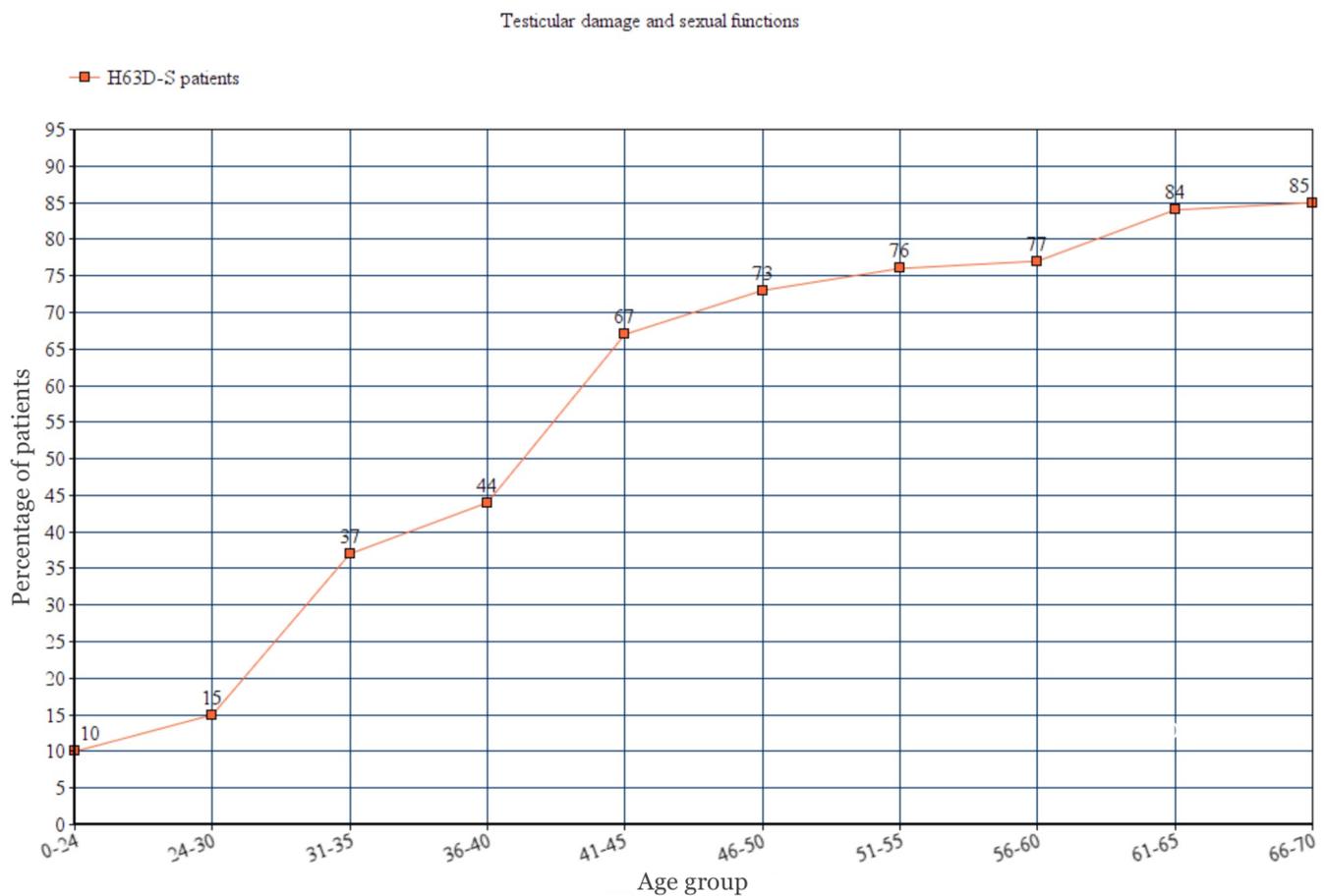
## Testicular damage in H63D patients

Since NTBI has a strong affinity for parenchymal tissue, the male gonads are a preferred target for this form of free iron. There, it penetrates the cells, causing oxidative damage and, as a consequence, non-dramatic but significant regressive damage to the testes. On sonography (including Doppler), the tissue appears homogeneous, but a mild form of microlithiasis can be seen with more modern

sonography equipment, usually built after ~2015. Older sonography devices may miss microlithiasis because the calcifications are often too small for their resolving power.

Patients with microlithiasis should be followed up closely for quite a period of time, especially if under 45 years of age, as microlithiasis can occasionally be a sign of testicular cancer or an early warning sign of this undesirable condition.<sup>51,52</sup> Usually the damage is bilateral, we have not had a case where only one testicle was affected. The spermogram usually shows somewhat decreased fertility, but this has not become uncommon in the general male population anyway.

So far, we are not aware of any treatment that could stop the regressive process in H63D syndrome. However, since the effect is usually rather mild, few patients (or their partners) are likely to consider this a relevant problem. Therefore, this aspect of H63D syndrome is still largely unknown to urologists and andrologists.

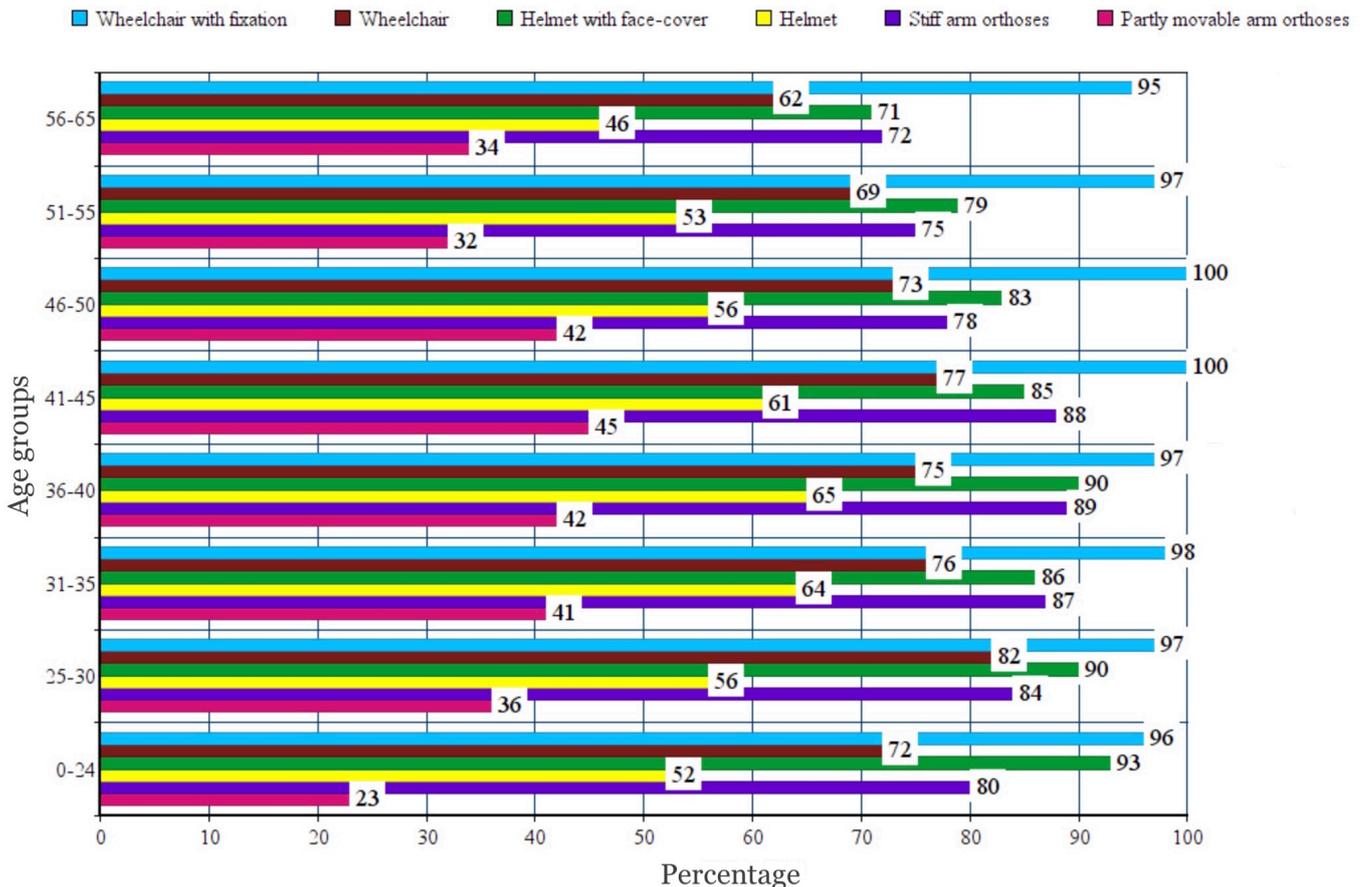


Currently, there are no known comparable symptoms due to NTBI on the female reproductive organs. However, screening as known from men has not been performed so far to our knowledge due to the lack of initial suspicion, the rarity of the disease and cultural barriers. According to the current state of research, however, such screening would be more in the interest of gender equity than medical necessity.

## Injury protection due to cataplexy per medical aid (*relative*)

As yet unpublished data suggest with near certainty that patients with advanced H63D syndrome are far worse off with medical aids than is the case, for example, with multiple sclerosis or epilepsy. This irresponsibly increases the risk of accidents and harm to H63D sufferers. They experience all kinds of damage from abrasions to fractures in the face and head area as a result of cataplexy, dizziness, tics, violent movements in REM sleep up to falls due to short "lapses" of body coordination. Nevertheless, assistive devices are very rarely prescribed. According to preliminary surveys, this has mainly to do with the fact that physicians are concerned about immobilizing patients too much in a condition that is rather unfamiliar to them. This concern is not only unfounded, it leads to a dangerous underuse of aids for patients with H63D syndrome. After all, one bad fall on a staircase or other hazardous location and you may treat a neck fracture in the emergency room.<sup>15,16,19,21</sup>

Protection against injuries in cataplexies in %



With these numbers and the risk to patients of serious injury, it can only be explained psychologically why many frontline physicians do not prescribe protection for their patients against the devastating consequences of their cataplexies and movement disorders. But the argument that prescribing wheelchair, orthoses, or helmets would not be necessary because H63D syndrome patients can walk is also absurd. It is good clinical practice to prescribe a wheelchair for patients with multiple sclerosis (MS) to

use whenever necessary. Seeing an MS patient walking part of the time and using his wheelchair part of the time is a most normal situation in neurology. The same is true for an infinite number of rarer neurological conditions. Why not for H63D syndrome patients as well? Not being too familiar with this rare syndrome is no excuse. In this day and age, all data is available online, so the only explanation, once again, is the conservatism of our profession.<sup>15-21</sup>

## Summary

Frontline clinicians should be aware of this symptom shift from often very severe tics in H63D syndrome to narcolepsy with cataplexy while all other symptoms of this very serious illness remain progressive:

- 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)
- Synucleinopathies of various degrees of severity (from mild cognitive impairment to dementia)
- 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)
- Variable skin symptoms (including impetigo, pruritus, hyperresponsiveness, etc.)
- Mild eosinophilia
- Rare: Renal involvement, ocular disease due to NTBI induced oxidative processes, hearing loss, etc.

## Conclusion

H63D syndrome is difficult to treat, always progressive and incurable. More research is needed, but we already know what we can do to supportively help our patients with off-label medications and medical devices. Currently, the greatest threat to patients with H63D syndrome still comes from colleagues who are unfamiliar with the disease. It is to be hoped that this will change as soon as possible.

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## Conflicts of interest

None declared.

## Ethical standards and patient's rights

This paper 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 by third parties 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 complied with. 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.

## Personal note

On the occasion of my departure from the International H63D Syndrome Research Consortium, I would like to thank all colleagues from around the world for their fantastic work and I am sure that H63D syndrome research will continue to be in good hands in the future. At the same time, I would like to express my gratitude to Dr. Marius Lazar, Dr. Carolina Diamandis and the entire team at LCG Greece, who have been incredibly helpful partners.

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