Symptom shift in 200 patients with H63D syndrome associated with abnormal TCS findings in substantia nigra

Jacob S. Adams  
International H63D Syndrome Research Consortium

Marianne Kaufmann  
International H63D Syndrome Research Consortium

Riku Honda  
International H63D Syndrome Research Consortium

Lucas Smith  
LCG Greece

David Seideman  
LCG Greece  
https://orcid.org/0000-0002-5749-5839

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Jacob S. Adams, Marianne Kaufmann, Riku Honda, Lucas Smith, David Seideman

Corresponding Authors

LCG Greece
H63D Syndrome Research Department
Dr. David Seideman & Dr. Lucas Smith
Kifissias 16, Athina, 115 26
Hellenic Republic
H63D@workmail.com

Abstract

In a study on the prevention of injury in patients with H63D syndrome and cataplexy, statistical analysis revealed an unexpected but clinically highly significant finding. Apparently, in this patient population, an inverse correlation exists between the severity of tic symptomatology on the one hand and narcolepsy with cataplexy on the other hand, as well as a parallel increase in the typical signs of degeneration observed in transcranial sonography of the substantia nigra. This finding has clinically far-reaching implications.
Tics, narcolepsy with cataplexy and TCS in H63D syndrome

Caused by a homozygous mutation of the HFE gene H63D, the so-called H63D syndrome is known for its diverse symptomatology. However, you will hardly find a H63D syndrome patient without tics, REM sleep disorders and/or narcolepsy with cataplexy, cardiac damage, liver dysfunction and not infrequently 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.14-18

![Fig.1 (TCS)](image)

Substantia nigra echogenicity (normal) in a healthy individual

Substantia nigra hyper-echogenicity as found in H63D syndrome

To investigate another aspect of this under-researched disease, we explored what type of protection is most effective for H63D syndrome patients cataplexy.49 To achieve this, we worked with two clinics in the Middle East and India affiliated with the International H63D Syndrome Research Consortium. The results were provided to us in anonymized form. As an unexpected finding, we became aware of an inverse correlation of motor symptoms and narcolepsy with cataplexy in direct correlation with findings on transcranial sonography (TCS) of the aforementioned type.

Method

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 using structured questionnaires about their symptoms, course of disease, other aspects of their condition; and each of them had at least one transcranial sonography with
modern equipment and physicians very highly trained for 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 ten (very hyper-echogenic substantia nigra).

Results

To our own surprise, we found a striking pattern consistent with the anecdotal description of disease progression as reported by the patients themselves:

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 narcolepsy with cataplexy. The differences between male and female patients are not significant.

The results of transcranial sonography were even more striking. Damage to the substantia nigra appears to correlate with the sharp increase in symptom severity of narcolepsy with cataplexy in patients with H63D syndrome, with tics decreasing the more substantia nigra damage becomes visible in TCS. To date, we have no satisfactory explanation for this finding. However, we propose to call the phenomenon the "Adams paradox," named after Jacob S. Adams, who was a pioneer in H63D syndrome research and is leaving the International H63D Syndrome Consortium for new academic perspectives.

Fig. 2
Discussion

The fact that the H63D syndrome does not fit into any pre-existing box has been obvious since the beginning of research on the subject. However, the finding of the "Adams paradox" has important consequences for diagnosis and treatment. For some time, there were discussions and attempts to control the motor symptoms of H63D syndrome patients with levodopa. Now, one of the side effects of levodopa is actually narcolepsy.47,48,50 However, we were in the fortunate position that 197 of our 200 patients were not taking levodopa or had never taken this substance. Thus, levodopa cannot explain the inverse correlation of symptom development. The strikingly similar course of damage to the substantia nigra and parts of the basal ganglia seen on transcranial sonography is a strong indication that the destruction and scarring in this brain region must underlie the answer to this highly interesting phenomenon.

At the same time, it should caution clinicians to be careful about administering levodopa to patients with H63D syndrome already at this early stage of research into the "Adams phenomenon," even if these patients show symptoms that are normally treated with this substance. If it cannot be avoided, additional precautions and close follow-up should be mandatory. To an outside observer, tics and symptoms of hyperkinesia may appear drastic, but the heavier burden on the patients is severe narcolepsy with cataplexy.4-8,15-17 We also recognize that damage to the substantia nigra, as is seen in TCS, does not necessarily equate to Parkinson's, although we know from as yet unpublished data that about one-third of patients with H63 syndrome develop Parkinson's-like symptoms after the age of 55.

Conclusion

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.

H63D syndrome is a difficult-to-treat, always progressive and incurable syndrome. However, with this knowledge, it should now be possible to avoid prescribing errors in the context of this challenging illness.

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