H63D Syndrome Research Consortium

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

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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]

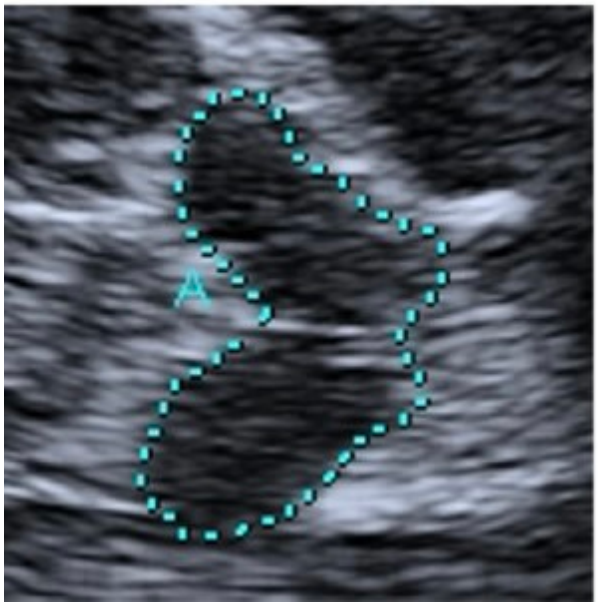
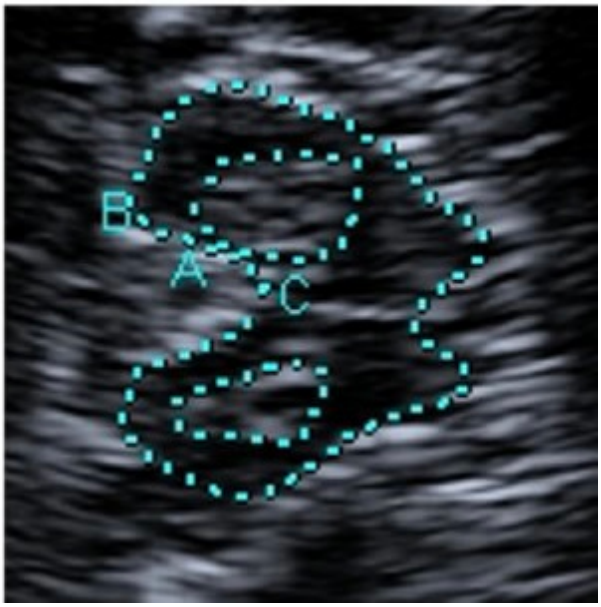


Fig.1 (TCS) Substantia nigra echogenicity (normal) in a healthy individual



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:

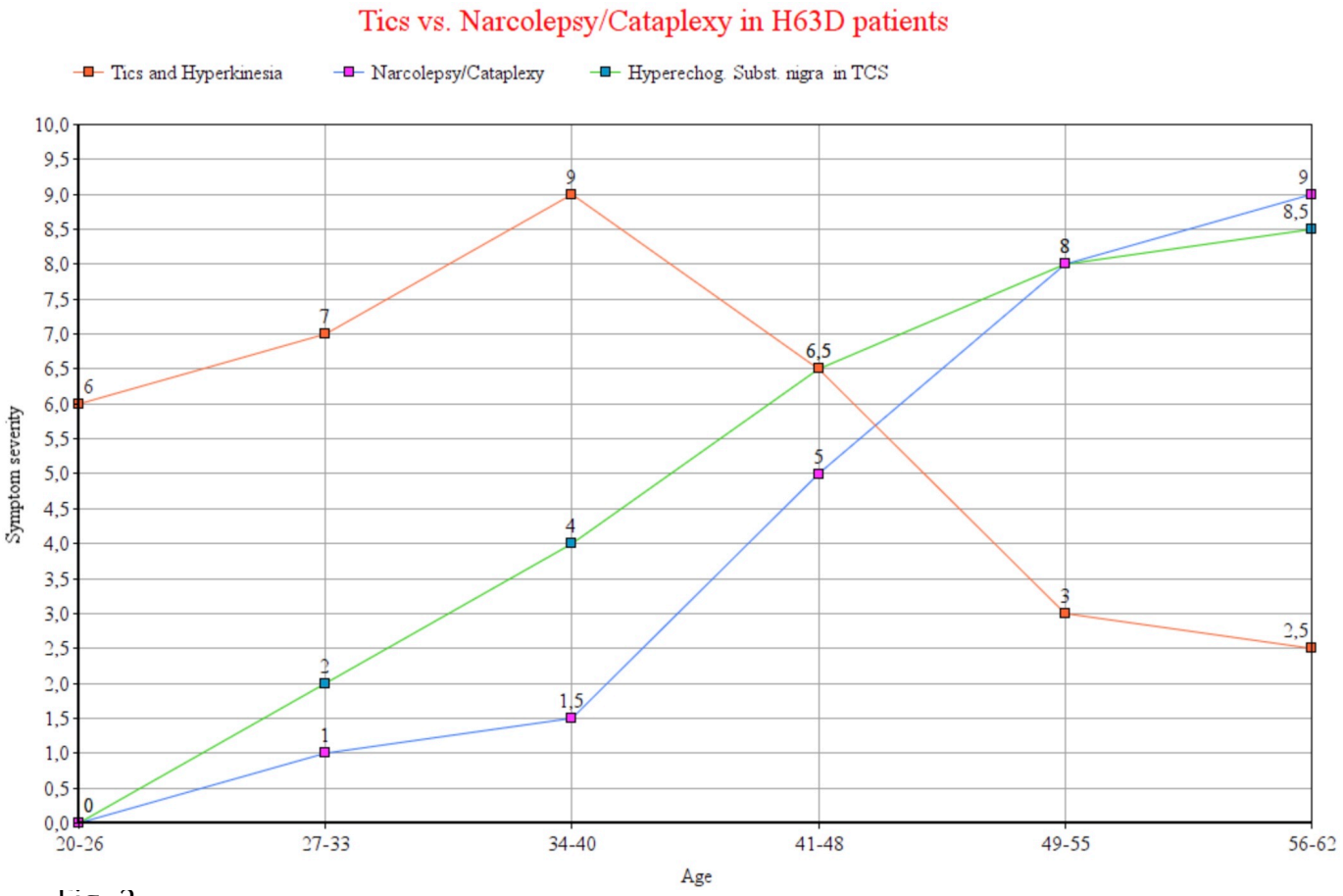


Fig. 2

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 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.

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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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 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.

References

1. Pizza F, Antelmi E, Vandi S, Meletti S, Erro R, Baumann CR, Bhatia KP, Dauvilliers Y, Edwards MJ, Iranzo A, Overeem S, Tinazzi M, Liguori R, Plazzi G. The distinguishing motor features of cataplexy: a study from video-recorded attacks. Sleep. 2018 May 1;41(5). doi: 10.1093/sleep/zsy026. PMID: 29425380.

2. Moturi S. DeWolfe JL. Isolated Cataplexy. In: Sleep Review Mag., 2010

3. Hartse KM, Zorick FJ, Sicklesteel JM, Roth T. Isolated cataplexy: a familial study. Henry Ford Hosp Med J, 1988;36(1):24-7.

4. Morgenthaler TI, Kapur VK, Brown T; Standards of Practice Committee of the American Academy of Sleep Medicine. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. Sleep. 2007;30:1705-11.

5. Reading P. Cataplexy. Pract Neurol. 2019 Feb;19(1):21-27. doi: 10.1136/practneurol-2018-002001. Epub 2018 Oct 24. PMID: 30355740.

6. Matos N, Gaig C, Santamaria J, Iranzo A. Cataplexy causing subdural hematomas. Sleep Med. 2017 Feb;30:15-16. doi: 10.1016/j.sleep.2016.01.018. Epub 2016 Mar 7. PMID: 28215239.

7. Adams R, Mayhew IG. Neurologic diseases. Vet Clin North Am Equine Pract. 1985 Apr;1(1):209-34. doi: 10.1016/s0749-0739(17)30778-2. PMID: 3000543.

8. Peacock J, Benca RM. Narcolepsy: clinical features, co-morbidities & treatment. Indian J Med Res. 2010 Feb;131:338-49. PMID: 20308759.

9. Pillen S, Pizza F, Dhondt K, Scammell TE, Overeem S. Cataplexy and Its Mimics: Clinical Recognition and Management. Curr Treat Options Neurol. 2017 Jun;19(6):23. doi: 10.1007/s11940-017-0459-0. PMID: 28478511.

10. Jory C, Oak K, Organ C, Mclean B, Shankar R. Head first - Review of epilepsy head injury risk and protection. Seizure. 2019 Oct;71:66-79. doi: 10.1016/j.seizure.2019.06.013. Epub 2019 Jun 12. PMID: 31207395.

11. Trefler E, Fitzgerald SG, Hobson DA, Bursick T, Joseph R. Outcomes of wheelchair systems intervention with residents of long-term care facilities. Assist Technol. 2004; 16(1):18–27. PMID: 15357146

12. LaPlante MP. Demographics of wheeled mobility device users. In: Proceedings of the Conference on Space Requirements for Wheeled Mobility; 2003 Oct 9–11; Buffalo (NY). Buffalo (NY): University at Buffalo, State University of New York; 2003.

13. Simpson RC et al. How many people would benefit from a smart wheelchair? In: Journal of Rehabilitation Research & Development. Volume 45, Number 1, 2008

14. Chang ET, Lin CL, Chen SF, Hsu CY, Shen YC. Risk of bone fractures in patients with narcolepsy: a nationwide population-based cohort study. Sleep Med. 2020 Jun;70:55-59. doi: 10.1016/j.sleep.2020.02.015. Epub 2020 Feb 26. PMID: 32197225.

15. Diamandis C, Tudor A: Medical devices that should be prescribed to patients with cataplexy to reduce their risk of injury. Authorea Publishing, 2021 doi: 10.22541/au.162187144.47184988/v1

16. Diamandis C, Adams Jacob S, Honda R, et al. Regularly missed symptoms in primary and secondary narcolepsy . Authorea Publishing, 2021 doi: 10.22541/au.162134961.11409756/v1

17. Seideman D et al. H63D Syndrome: What we know about it in 2021. Authorea Publishing, 2021 doi: 10.22541/au.162191694.46218714/v1

18. Sørensen S et al. H63D Syndrome: Consensus Paper of the International H63D Research Consortium, Oslo 2019

19. Deekollu et al. Seizure-related injuries in a group of young people with epilepsy wearing protective helmets: Incidence, types and circumstances, Seizure, Volume 14, Issue 5, 2005, Pages 347-353, ISSN 1059-1311, doi.org/10.1016/j.seizure.2005.04.008.

20. Camfield C, Camfield P. Injuries from seizures are a serious, persistent problem in childhood onset epilepsy: a population-based study. Seizure. 2015 Apr;27:80-3. doi: 10.1016/j.seizure.2015.02.031. Epub 2015 Mar 6. PMID: 25891933

21. Wirrell EC. Epilepsy-related injuries. Epilepsia. 2006;47 Suppl 1:79-86. doi: 10.1111/j.1528-1167.2006.00666.x. PMID: 17044832.

22. Frey K, Zöllner JP, Knake S, Oganian Y, Kay L, Mahr K, Keil F, Willems LM, Menzler K, Bauer S, Schubert-Bast S, Rosenow F, Strzelczyk A. Risk incidence of fractures and injuries: a multicenter video-EEG study of 626 generalized convulsive seizures. J Neurol. 2020 Dec;267(12):3632-3642. doi: 10.1007/s00415-020-10065-5. Epub 2020 Jul 10. PMID: 32651672; PMCID: PMC7674387.

23. Kostas Pantopoulos: Inherited Disorders of Iron Overload. Front. Nutr. 5:103. doi: 10.3389/ fnut.2018.00103

24. Wint Nandar, James R. Connor: HFE Gene Variants Affect Iron in the Brain. The Journal of Nutrition, Volume 141, Issue 4, April 2011

25. Dekker MC, Giesbergen PC, Njajou OT, van Swieten JC, Hofman A, 127. Breteler MM, van Duijn CM. Mutations in the hemochromatosis gene (HFE), Parkinson's disease and parkinsonism. Neurosci Lett. 2003;348:117–119

26. Steven M. LeVine, James R. Connor, Hyman M. Schipper: Redoxactive Metals in Neurological Disorders. New York Academy of Sciences, 2004.

27. Sareen S. Gropper, Jack L. Smith, Timothy P. Carr: Advanced Nutrition and Human Metabolism. Cengage Learning, 7th edition, Boston 2016.

28. Bartzokis G, Lu PH, Tishler TA, Peters DG, Kosenko A, Barrall KA, Finn JP, Villablanca P, Laub G, Altshuler LL, Geschwind DH, Mintz J, Neely E, Connor JR: Prevalent iron metabolism gene variants associated with increased brain ferritin iron in healthy older men. J Alzheimers Dis. 2010 Apr;20(1):333–341.

29. Brissot P, Ropert M, Le Lan C, Loreal O. Non-transferrin bound iron: a key role in iron overload and iron toxicity. BBA Gen Subjects (2012) 1820:403–10. doi: 10.1016/j.bbagen.2011.07.014

30. Athiyarath R, Arora N, Fuster F, Schwarzenbacher R, Ahmed R, George B, et al. Two novel missense mutations in iron transport protein transferrin causing hypochromic microcytic anaemia and haemosiderosis: molecular characterization and structural implications. Br J Haematol. (2013) 163:404– 7. doi: 10.1111/bjh.12487

31. Akbas N, Hochstrasser H, Deplazes J, Tomiuk J, Bauer P, Walter U, Behnke S, Riess O, Berg D.: Screening for mutations of the HFE gene in Parkinson's disease patients with hyperechogenicity of the substantia nigra. Neurosci Lett. 2006

32. Borie C, Gasparini F, Verpillat P, Bonnet AM, Agid Y, Hetet G, Brice A, Durr A, Grandchamp B.: Association study between iron-related genes polymorphisms and Parkinson's disease. J Neurol. 2002; 249: 801–804.

33. Guerreiro RJ, Bras JM, Santana I, Januario C, Santiago B, 120. Morgadinho AS, Ribeiro MH, Hardy J, Singleton A, et al.: Association of HFE common mutations with Parkinson's disease, Alzheimer's disease and mild cognitive impairment in a Portuguese cohort. BMC Neurol. 2006;6:24

34. Fujii H, Takagaki N, Yoh T, Morita A, Ohkawara T, Yamaguchi K, Minami M, Sawa Y, Okanoue T, Ohkawara Y, Itoh Y: Non-prescription supplement-induced hepatitis with hyperferritinemia and mutation (H63D) in the HFE gene. Hepatol Res. 2008 Mar;38(3):319–323

35. Castiella, Urreta, Zapata et al.: H63/H63D genotype and the H63D allele are associated in patients with hyperferritinemia to the development of metabolic syndrome. Eur J Intern Med. 2019 Nov 30. doi:10.1016/j.ejim.2019.11.021

36. Gkouvatsos K, Papanikolaou G, Pantopoulos K. Regulation of iron transport and the role of transferrin. Biochim Biophys Acta (2012) 1820:188–202. doi: 10.1016/j.bbagen.2011.10.013

37. Mitchell RM, Lee SY, Simmons Z, Connor JR: HFE polymorphisms affect cellular glutamate regulation. Neurobiol Aging. 2009

38. Wint Nandar, James R. Connor: HFE Gene Variants Affect Iron in the Brain. The Journal of Nutrition, Volume 141, Issue 4, April 2011, 729S–739S, doi:10.3945/jn.110.130351

39. Borie C, Gasparini F, Verpillat P, Bonnet AM, Agid Y, Hetet G, Brice A, Durr A, Grandchamp B.: Association study between iron-related genes polymorphisms and Parkinson's disease. J Neurol. 2002; 249: 801–804

40. Steven M. LeVine, James R. Connor, Hyman M. Schipper: Redoxactive Metals in Neurological Disorders. New York Academy of Sciences, 2004

41. Valenti L, Fracanzani AL, Bugianesi E, Dongiovanni P, Galmozzi E, Vanni E, Canavesi E, Lattuada E, Roviaro G, Marches G, Fargion S.: HFE genotype, parenchymal iron accumulation, and liver fibrosis in patients with nonalcoholic fatty liver disease. Gastroenterology. 2010 Mar;138(3):905–912.

42. P. Adams, P. Brissot, L. W. Powell: EASL International Consensus Conference on Haemochromatosis. Journal of Hepatology 2000;33:485–504.

43. de Valk, Addicks, Gosriwatana et al.: Non-transferrin-bound iron is present in serum of hereditary haemochromatosis heterozygotes. Eur J Clin Invest. 2000 Mar;30(3):248-51

44. Jakeman A, Thompson T, McHattie J, Lehotay DC: Sensitive method for nontransferrin-bound iron quantification by graphite furnace atomic absorption spectrometry. Clin Biochem. 2001 Feb;34(1):43-7

45. Nakamura M, Nishida S, Hayashida K, Ueki Y, Dauvilliers Y, Inoue Y. Differences in brain morphological findings between narcolepsy with and without cataplexy. PLoS One. 2013 Nov 28;8(11):e81059. doi: 10.1371/journal.pone.0081059. PMID: 24312261; PMCID: PMC3842956

46. Kumar S, Sagili H. Etiopathogenesis and neurobiology of narcolepsy: a review. J Clin Diagn Res. 2014 Feb;8(2):190-5. doi: 10.7860/JCDR/2014/7295.4057. Epub 2013 Dec 27. PMID: 24701532; PMCID: PMC3972560

47. Hauser RA. Levodopa: past, present, and future. Eur Neurol. 2009;62(1):1-8. doi: 10.1159/000215875. Epub 2008 Sep 9. PMID: 19407449

48. Jankovic J. Levodopa strengths and weaknesses. Neurology. 2002 Feb 26;58(4 Suppl 1):S19-32. doi: 10.1212/wnl.58.suppl_1.s19. PMID: 11909982

49. Seideman D, Adams JS, Honda R, Smith L, Diamandis C. Injury protection strategies for H63D syndrome patients suffering from cataplexy. Zenodo Publishing, 2021 doi.org/10.5281/zenodo.4812970

50. Black SW, Yamanaka A, Kilduff TS. Challenges in the development of therapeutics for narcolepsy. Prog Neurobiol. 2017 May;152:89-113. doi: 10.1016/j.pneurobio.2015.12.002. Epub 2015 Dec 23. PMID: 26721620; PMCID: PMC5114175