GRASSROOT SCIENCE COOPERATION
BY LCG GREECE & THE JEWISH UNIVERSITY (JUC)

Lucas Smith[1,2], **Sofia Makri**[2], **Benjamin Steinberg**[3], **Nicolas Kipper**[3], **Marius Lazar**[1], **Carolina Diamandis**[1]

1) LCG Greece Research
2) Lazar | Seideman | Smith JUC Training Practice Europe (South)
3) Jewish University (JUC), Faculty III

Corresponding office:
LCG Greece, Team of Dr. Carolina Diamandis
16 Kifisias Avenue, 115 26 Athens, GR-EU
research@lazar-consortium.com

Endocrinology

The utmost importance of ALPRAZOLAM in the treatment of NTBI-induced hyperadrenalism with epinephrine peaks and chronically elevated blood levels of adrenaline in rare degenerative diseases such as H63D syndrome

Abstract

In 1992, our esteemed colleagues Alan Breier, Orlando Davis, Robert Buchanan, Samuel J. Listwak, Courtney Holmes, David Pickar, and David S. Goldstein published a seminal scientific paper titled "Effects of Alprazolam on Pituitary-Adrenal and Catecholaminergic Responses to Metabolic Stress in Humans." In it, they described with high accuracy the effects of benzodiazepines on stress-induced activation of the three classic "stress" systems: Pituitary-adrenal, adrenal medullary, and sympathoneural systems. The results provided an answer to a question that is still being asked today: Why is alprazolam so much more effective than all other benzodiazepines for certain anxiety-related conditions, especially panic attacks? The colleagues found the answer to that question, but although the work was impeccable, their findings never made it into medical textbooks. What Breier et al. found was this: Alprazolam is able to attenuate 2DG-induced activation of the HPA axis and adrenomedullary activity, as evidenced by attenuated responses of plasma levels of ACTH and epinephrine, respectively, without clinically affecting other important responses of two indices of sympathoneural activity. For the treatment of patients whose adrenal glands are working in a highly dysfunctional or centrally dysregulated manner due to rare diseases such as NTBI induced H63D syndrome, alprazolam is still the first drug of choice - despite its dependence potential - to protect the organism of the affected person from dangerous adrenaline excesses.

NTBI and H63D syndrome

Only very rarely a homozygous mutation of the HFE gene H63D can lead to hemochromatosis. Therefore, this mutation is usually wrongly considered clinically not very relevant in comparison to other HFE mutations. However, this is not correct. We reported typical symptom constellations in patients with a homozygous mutation of the HFE gene H63D who have developed H63D syndrome in an earlier study. Unlike what is the case in hemochromatosis, the syndrome does not result from ferritin overload but from accumulation of non-transferrin-bound iron (NTBI) caused by a trigger-unresponsive hypotransferrinemia.[2,7,26]

NTBI has the ability to enter numerous cell types and calcium channels. In the cells, it leads to degeneration processes. In advanced stages, therefore, brain damage (especially in the substantia nigra and basal ganglia), cardiac muscle damage or conduction disorders (e.g. heart blocks) may occur. In the cells, NTBI leads to oxidation processes that damage or destroy the affected cells affected and variable dysfunction of the liver are also among the symptoms found in H63D syndrome. The skin shows hyperresponsiveness, and urologists find mildly atrophic testes in affected men.The brain, heart, liver, skin and, in males the testes are virtually always affected.[1-7]

H63D syndrome is still an incurable multi-organ disease, leading to permanent and often severe disability, which can only be influenced by early diagnosis and a very careful reduction of iron intake (under constant medical monitoring) as early as in childhood and youth. Phlebotomies or dialysis are ineffective in this disease. Bloodletting only causes further loss of vital ferritin. Dialysis does also not lead to a clinically favorable result. The NTBI type iron remains in the cells until they die, only to immediately "move" to a nearby cell. Filtering NTBI from the blood is possible, but due to the described behavior of NTBI, the success would be very limited.[15,20]

Another factor makes the procedure of dialysis completely useless in H63D syndrome: the basic pathomechanism of the disease is a quite dangerous non-responsive hypotransferrinemia. Since patients with H63D syndrome also need ferritin for survival, a completely iron-free diet is out of the question. Therefore, the "success" of any filtering of NTBI from the blood would be nullified with the next meal. The fact that some physicians nevertheless recommend phlebotomies or filtration therapies can at best be explained by a lack of knowledge. In any case, it is to be warned against it.[2,5-7]

Catecholamines, adrenal afflictions and stress axis dysregulations in the context of H63D syndrome and adrenal glands damaged by other noxious agents

One aspect of H63D syndrome and other NTBI-driven disorders that has long received far too little attention is damage to the adrenal glands and to the regulatory circuits known as "stress axes" of the part of the catecholamine balance and certain hormones that are supposed to protect healthy people in moments of danger. Something by the lightning-like up-regulation of attention and strength to escape, to describe only the most prominent of the many ways. Adrenaline and cortisol play paramount roles in this process. Without the ability to synthesize adrenaline and to flood the body with it in a flash, man would probably have died out already in the times of the saber-toothed tiger due to fearless naivety as prey. Adrenaline, produced primarily in the renal medulla, is thus irreplaceably important. But as always, the dose makes the poison.

The human organism is not designed to cope with states of sustained pulses or even constantly elevated levels of adrenaline in the blood. Severe symptoms can result, especially cardiovascular and metabolic. Patients with advanced H63D syndrome are particularly often affected by too much adrenaline in the

organism due to NTBI-related damage to the adrenal medulla, often also to the pituitary gland and the dysregulation of the essential feedback mechanisms. This leads, once occurred, to further organ damages, not only by NTBI, but obviously also quite directly by a constantly too strong load with by adrenalin and cortisol.

Relaxation courses, yoga, psychotherapy and other popular measures do not help this group of people, whom the dysregulations are the consequence of an organic damage. From it a vicious circle develops, and not rarely apparently further illnesses like at the metabolic syndrome, which is basically however in this case with identical symptoms the consequence of too high catecholamine values, above all the Adrenalin. Reducing this level with medication is a therapeutic inevitability in the example mentioned. However, the choice of those drugs which reduce adrenaline synthesis in the renal medulla by 40-70% is rather limited, to put it mildly.

Discussion

This is where the unfortunately forgotten findings of Breier et al (1992) come into play. For the administration of 2 to 10mg of alprazolam per day, depending on the patient's findings, sex, height and weight, divided into 3 to 5 single doses can actually reduce the excessive and uncontrolled amount of epinephrine pulsing into the body by 40-75%. In a sample of our own patients with H63D syndrome, the drop in adrenaline synthesis in the adrenal gland averaged 55% after the first few have. Peak reductions of up to 87% could be achieved without significant side effects. In a H63D syndrome collective of n=14 (8 men and 6 women) reductions of 72.8% on average were achieved. At the same time, other aspects of the SNP/SAM axis slowly normalized. The clinical condition increased by more than 50% for the better, only one patient discontinued the treatment with an average of 6 mg alprazolam per 24 hours, because aggression appeared as side effects. Of the remaining test group, 9 patients then took alprazolam as part of their standard medication without dose escalation, the remaining three wanted to participate in another study and had no problems discontinuing alprazolam in stages within 8 weeks under medical supervision.[1-29,30]

Conclusion

Patients with H63D syndrome often suffer from NTBI-induced damage to the adrenal glands, cerebral control of stress axes, and the resulting sequelae. Usual relaxation procedures are of no use at all with this hard organic finding, adrenaline in constant elevation stresses a number of metabolic processes (fats, sugars, even the uptake of secondary plant compounds) which is beyond the scope of this paper. Alprazolam, and strictly speaking only this substance, is the drug of first choice in this situation. Its benefits undoubtedly outweigh its risks in this off-label use, including the risk of a protracted discontinuation syndrome. With this problem, however, alprazolam is not a singularity. An overly casual approach in the 1980s and as one of the youngest benzodiazepines, it was soon described as particularly disadvantageous due to its high potency and short half-life, and was marketed listlessly against opposition, especially outside the USA, whose reverberations continue to provoke irrational reflexes and policies in Europe, for example, to this day.

Legal risks and unethical behavior by avoiding prescribing alprazolam

In contrast, we advise the medically strictly supervised but courageously dosed use of alprazolam as a drug for an overactive renal medulla, stress axis disorders and organically induced anxiety sensations as the drug of first choice. Treatment should be by an experienced physician who has no fear of contact with the use of benzodiazepines.
Avoiding the use of alprazolam as a direct inhibitor of adrenaline synthesis as an off-label medication in the context of rare diseases solely because of a potentially possible

discontinuation syndrome at the conceivable end of a treatment would be, at least medically, an act of omission, since no other drug with exactly this effect is available for the exactly relevant cells. Theoretical side effects, which are manageable, cannot be a reason to disregard a very safe[31], effective and approved drug. After all, one does not deny a type 1 diabetic his insulin just because it may have adverse long-term consequences. Why should one do act differently in the case of adrenalin and alprazolam?

Conflicts of interest

None declared.

Funding & other types of support

a) Jewish University of Colorado, Faculty III
b) DRBIM Social Micro Investments
c) EAP Pharmacy
d) PlusOne Israel
e) Beurer Germany
f) SD Biosensor
g) ABIN Medical Department 12
h) PGP legal department

Acknowledgement

We thank Professor Dr. Wilhelm Krone of Cologne (Köln) Germany and Prof. Dr. David Seideman for their outstanding counsel and very helpful interest in the main topic of this paper. Their expertise was, is and will continue to be unparalleled.

References

1. Kostas Pantopoulos: Inherited Disorders of Iron Overload. Front. Nutr. 5:103. doi: 10.3389/fnut.2018.00103
2. Wint Nandar, James R. Connor: HFE Gene Variants Affect Iron in the Brain. The Journal of Nutrition, Volume 141, Issue 4, April 2011
3. 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.
4. Steven M. LeVine, James R. Connor, Hyman M. Schipper: Redoxactive Metals in Neurological Disorders. New York Academy of Sciences, 2004.
5. Sareen S. Gropper, Jack L. Smith, Timothy P. Carr: Advanced Nutrition and Human Metabolism. Cengage Learning, 7th edition, Boston 2016.
6. 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.
7. 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
8. 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
9. 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;407:16–19.
10. 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.
11. 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.

12. 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.
13. 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.
14. 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.
15. 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
16. Mitchell RM, Lee SY, Simmons Z, Connor JR: HFE polymorphisms affect cellular glutamate regulation. Neurobiol Aging. 2009.
17. 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
18. 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.
19. Steven M. LeVine, James R. Connor, Hyman M. Schipper: Redoxactive Metals in Neurological Disorders. New York Academy of Sciences, 2004.
20. Valenti L et al.: HFE genotype, parenchymal iron accumulation, and liver fibrosis in patients with nonalcoholic fatty liver disease. Gastroenterology. 2010 Mar;138(3):905–912.
21. P. Adams, P. Brissot, L. W. Powell: EASL International Consensus Conference on Haemochromatosis. Journal of Hepatology 2000;33:485–504.
22. Iron Disorders Institute nanograms: H63D - Other Mutation. April 2010
23. 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.
24. G. M. Bishop, T. N. Dang, R. Dringen, S. R. Robinson: Accumulation of Non-Transferrin-Bound Iron by Neurons, Astrocytes, and Microglia. In: Neurotoxicity Research. 19, 2011, S. 443–451, doi:10.1007/s12640-010-9195-x.
25. 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
26. Diamandis C, Adams J, Seideman D, et al.: H63D-Syndrome: A phenotype caused by a homozygous mutation of HFE gene H63D. April 2021.
27. M. Kelley, N. Joshi, Y. Xie, M. Borgaonkar: Iron overload is rare in patients homozygous for the H63D mutation. In: Canadian Journal of Gastroenterology & Hepatology. April 2014, doi:10.1155/2014/468521
28. A. Finkenstedt, M. Schranz, N. Baumgartner et al.: HFE Genotypen, Eisenstatus und Überleben. In: Zeitschrift für Gastroenterologie, Vol. 52 – P65, 2014, doi:10.1055/ s-0034-1376049.
29. L. Valenti, A. L. Fracanzani, E. Bugianesi, P. Dongiovanni, E. Galmozzi, E. Vanni, E. Canavesi, E. Lattuada, G. Roviaro, G. Marchesini, S. Fargion: HFE genotype, parenchymal iron accumulation, and liver fibrosis in patients with nonalcoholic fatty liver disease. In: Gastroenterology. Vol. 138, No 3, March 2010, S. 905–912, doi:10.1053/ j.gastro.2009.11.013, PMID 19931264
30. Working group data. To be published after the peer-review process.
31. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury (www.livertix.nih.gov)