Posted on 26 Oct 2022 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.166679630.07413034/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

Ongoing clinical observation of significance #2.7 - Rapid Corticosteroid-induced reduction of blood glucose level in a patient with a hereditary iron transport disorder H63D syndrome

Dr. Carolina Diamandis[1], David Seideman[1], Lucas Smith[1], Sofia Makri[1], Benjamin Steinberg[1], Martin Gangnon[1], Adrian Tudor[1], and Olga Ivanova[1]

[1]Affiliation not available

October 26, 2022

Abstract

Update 2.7

We report the case of a patient who suffers from hypotransferrinemia due to a genetic defect, subsequently suffers organ damage due to non-transferrin bound iron (NTBI) and develops a paradoxical reaction of glucose metabolism as a result of treatment with corticosteroids. To our knowledge, this is the first description of such an effect in the medical literature. The mechanism and further course of this phenomenon are currently still in the dark. Due to its peculiarity, we therefore publish only the clinical key data for the time being. We reported earlier about the same patient's change in his narcolepsy symptoms.

David Seideman[2,3], **Lucas Smith**[1,2], **Sofia Makri**[2], **Benjamin Steinberg**[3], **Martin Gangnon**[2,3], **Adrian Tudor**[5], **Olga Ivanova**[1], **Carolina Diamandis**[1]

1) LCG Greece Research
2) Lazar | Seideman | Smith JUC Training Practice
3) Jewish University (JUC), Faculty III
4) LAZAR | SEIDEMAN | SMITH - JUC Teaching Facility Luxembourg
5) privateGP Europe

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

Ongoing Clinical observation of significance #2.7

Rapid Corticosteroid-induced reduction of blood glucose level in a patient with a hereditary iron transport disorder H63D syndrome

Abstract

We report the case of a patient who suffers from hypotransferrinemia due to a genetic defect, subsequently suffers organ damage due to non-transferrin bound iron (NTBI) and develops a paradoxical reaction of glucose metabolism as a result of treatment with corticosteroids. To our knowledge, this is the first description of such an effect in the medical literature. The mechanism and further course of this phenomenon are currently still in the dark. Due to its peculiarity, we therefore publish only the clinical key data for the time being. We reported earlier about the same patient's change in his narcolepsy symptoms.

Rapid paradoxical response of a patient's glucose metabolism to the treatment with oral corticosteroids

A short-term administration at a maximum dose of up to 35 mg/d prednisolone (orally), adjunctive to outpatient surgical treatment of a severe acne inversa flare, led to foudroyant complications in a male patient (47/ European) suffering from a genetic iron metabolism disorder (H63D syndrome), who had not taken oral corticosteroids for 26 years.[1-7] The emergence of these remarkably

severe and odd complications was caused by a sudden decompensation of a largely masked adrenal insufficiency, primary but non-Addison in nature. (The details will be disclosed in a proper case study when the test and trial phase will have been rightfully considered accomplished). After the patient was clinically stable again, therapy with prednisolone was continued at a slightly lower dose (50%) and in a different pattern. Further investigations followed, which showed that additional adrenaline surges occurred that were too strong and lasted too long to be considered physiological. Moreover, the picture that emerged was of both a SAM and HPA axis that had been in pathological homeostasis prior to the unmasking prednisolone treatment due to NTBI (iron) damage to central structures of the organ. Indeed, there was evidence in the patient's medical record of a chaotic state of stress hormones, particularly adrenaline, and catecholamine secretion. We assume that the external treatment team at that time was simply unable to correctly interpret, let alone treat, this highly complex and quite rare pathological constellation.

Due to the onset of edema at the lacrimal sacs (bilateral), we switched the patient from prednisolone to dexamethasone 3x 0.5 mg per day, as this corticosteroid has no mineralcorticoid effects. Despite his concerns about side effects, the patient responded well to this low dose. However, his social environment made him fearful of taking the drug, and the ubiquitous warnings about the dangers of corticosteroids on the internet were certainly not helpful in optimizing compliance either. So we switched him to the more "natural" hydrocortisone, which caused a series of new issues after a few days due to its short half-life and mineralcorticosteroid properties. The lacrimal sac edema became swollen again, the patient's chronic constipation became unbearable, and his blood glucose levels again became unbalanced. After switching to dexamethasone, the lacrimal edema slowly resolved as expected and the effects we had seen with prednisolon were robust again.

We also learned that the patient's panic-like awakenings (as if from a nightmare with rapid pulse, blood pressure, glucose >120mg/dl) were not fully manageable with any of the corticosteroid alone. Since the last report, we have therefore added Xanax (alprazolam) to the patient's medication regimen because, despite its poor reputation as an addictive psychotropic drug, it is the only hyper-rapid acting adrenalin suppressor (up to 50%) with direct action on the medulla glandulae suprarenalis.[10] Given that the patient had been stable on another benzodiazepine for years anyway, the partial switch to Xanax posed no new risk of developing dependence or entering completely new territory.

The Xanax effect was immediate and appears to be robust at present. Ex juvantibus, combined with multiple tests, we are now certain that the patient's SAM axis is at least as dysfunctional as his HPA axis.

Furthermore, we are currently observing another paradoxical effect: the patient's blood lipid levels decrease when taking dexamethasone, LDL quite significantly, triglycerides even dramatically (about -50%), in fasting state as well as postpradnially. We have not yet come to any preliminary classification of this observation, but we are pleased to accept it and monitor it very closely.

Of particular scientific interest is also another phenomenon: after several extremely different meals, the patient's blood glucose values occasionally shot up to around 160 to 180 mg/dl, with a peak about 3 to 4 hours after the food intake, followed by an unshakable plateau phase when the steroid dose was too low or the patient forgot to take one of the dexamethasone doses. In these moments, we have now seen several times that 0.5 to 0.75 mg of dexamethasone (taken orally) resolved the situation within 15 to 45 minutes. Generally, within minutes of the onset of dexamethasone action, we achieved a drop in blood glucose to levels between 80 and 100 mg/dl. In some cases, this even corresponded to a drop to 70, 80, or even 90 mg/dl within a few minutes. In

these cases, the only symptom reported by the patient was that he felt quite warm. However, this subsided again as soon as the sugar level returned to the normal range.

Our team of clinicians has also made some progress in evaluating the pharmacodynamic effects at different dosage patterns. A rather unusual regimen of 0.5 mg dexamethasone immediately after awakening along with 1 mg Xanax, and with a mandatory second dose of 0.75 mg dexamethasone together with 0.5 mg Xanax after just 2 hours has so far shown the strongest effect on all desired effects until 5:00 (17:00) in the afternoon. At present, it appears that a further administration of 2 mg Xanax in the late afternoon is necessary, consistent with the half-life of the drug. Most likely, another 0.5 mg of dexamethasone after dinner will be necessary. We will report on this in a follow-up paper.

What we see, however, is as amazing as it can get: We see that administration of low doses of dexamethasone (plus alprazolam/ Xanax as a potent epinephrine blocker) in a middle-aged male patient can, for reasons yet to be explored, bring pathological blood glucose levels (as well as high levels of triglycerides and cholesterol) and disturbed HPA and SAM axes into physiological balance in this regard. This paradoxical effect of a highly potent corticosteroid and an epinephrine blocker, hitherto completely unknown in medicine, can already be considered confirmed.

Nevertheless, this report is in no way intended to encourage other clinicians to try this treatment in their patients even now. We enjoy the privilege of working under very specific conditions with means and tools that are not available even in some of the best university hospitals. This report, therefore, merely describes a hitherto completely unknown effect in a person suffering from a severe metabolic disorder. We strongly discourage our own experiments until we can publish more details. Our task, and that of all clinicians and scientists, should now be to determine the mechanism responsible for this totally unexpected effect and to find ways of safely treating similar patients with low therapeutic doses of dexamethasone and an epinephrine/ adrenaline inhibitor, while trying to minimize the unfavorable effects of the two substances mentioned.

Conflicts of interest

None declared.

Funding and/or other support

a) Jewish University of Colorado, Faculty III
b) LCG Greece
c) Luzia Healthcare Society
d) Roche
e) Beurer

Acknowledgement

We thank Professor Dr. Wilhelm Krone of Cologne (Köln) Germany for his outstanding counsel and very helpful interest in this case. His expertise was, is and will continue to be internationally unparalleled.

References

1. Banaszkiewicz et al.: Endocrine disorders in patients with hereditary hemochromatosis European Journal of Translational and Clinical Medicine, 2018
2. Papadopoulos et al.: Prevalence of Narcolepsy in Patients with H63D Syndrome Sys Rev Pharm, 2021
3. Seideman D, Adams JS, Honda R, Smith L, Diamandis C: Injury protection strategies for H63D syndrome patients suffering from cataplexy. Zenodo Online Publishing. Geneva, 2021
4. Carolina Diamandis, David Seideman, Smith Lucas. H63D: The Other Mutation (2021 version). Authorea. November 29, 2021
5. Carolina Diamandis, William Smith, Marianne Kaufmann, et al. H63D-Syndrome: Quick Reference Guide. Authorea. December 16, 2021
6. Anderson, G.J. 1999 Non-transferrin-bound iron and cellular toxicity. Journal of Gastroenterology and Hepatology, 14, 105
7. M. Kaufmann, R. Honda et al. (2021) Incidence of a clinically relevant H63D

syndrome in carriers of a homozygous mutation of HFE gene H63D.
8. Schubert M, Gautam D, Surjo D, Ueki K, Baudler S, Schubert D, Kondo T, Alber J, Galldiks N, Küstermann E, Arndt S, Jacobs AH, Krone W, Kahn CR, Brüning JC. Role for neuronal insulin resistance in neurodegenerative diseases. Proc Natl Acad Sci U S A. 2004
9. Müller-Wieland D, Krone W. Prinzipien zur Therapie von Fettstoffwechselstörungen in der klinischen Praxis [Hyperlipidemia: therapeutic principles in clinical practice]. Med Klin (Munich). 2003
10. Breier A, Davis OR, Buchanan RW. Alprazolam attenuates metabolic stress-induced neuroendocrine and behavioral effects in humans. Psychopharmacology (Berl). 1991.