# Review of: "The Mechanism of Hyperammonemia Triggered by Corticosteroid Administration in Late-Onset Ornithine Transcarbamylase Deficiency"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

This study is very important for clinicians and patients. However, there are many issues to be resolved for publication. Please review it carefully.

## Major points

1. Title does not appropriate. Your data did not present the mechanism directly and lack of data. Hence, please change your title(ex. Corticosteroid changes gene expression associated urea cycle in OTCD etc.…)
2. The purpose of this study to evaluate the effect of corticosteroids on urea cycle enzyme expression and urea cycle-associate metabolites. However, you mentioned in abstract and introduction that The mechanism has been considered nitrogen overload due to the catabolic effect of corticosteroids. Hence, you have to investigate or analyze for catabolic and anabolic state before and after DEX administration in OTC mice. Gene expression and metabolic analysis related with catabolism/anabolism(ex. Autophagy, mTOR, PI3K, S6K, eIF-4E, 4E-BP1, eIF-4E etc) and pathological change in muscle and liver should be included in data at least. If not, it never to be concluded any result.
3. Introduction is insufficient and please included more information related with corticosteroid and metabolism to urea cycle.
4. Your data including Case series and animal investigation and these presentation is very confusing for us. Two cases in this study, there are no any amino acid change nor other metabolome analysis. In addition, you mentioned that corticosteroid causes hyperammonemia is well known, clinical presentation is not needed for this study. Please change the composition of this manuscript (eg. Move clinical presentation to supplemental data or delete it and/or to the other case reports journal)
5. Figure 3 dose not any new data in this study and already established data in. Hence, this figure should be deleted.
6. Discussion is extremely poor. You have to consider not only liver and also both kidney muscle and intestine metabolism. Plasma amino acids are maintain by collaboration with these all tissue and you have to investigate metabolomic analysis or consider them if you cannot do it.

## Minor points

1. In abstract, you wrote “by the loss of function in any of the enzymes associated with ureagenesis.”, which is true but confusing. Loss of function means functional loss and does not include deletion in genetic science. In addition, “in any of the enzymes” is also confusing. In urea cycle disease, the each specific enzyme should be reliable for the each disease. Hence, please change this sentence appropriately.
2. In abstract, you wrote “Corticosteroid is well known to induce life-threatening hyperammonemia”. However, that is not concluded, only suggested to avoid it. Hence, you have to change this sentence appropriately.
3. “Urea cycle disorders (UCDs)” is written in Background and also abstract.
4. In material and method of biochemical analyses, you wrote that serum levels of ammonia were measured using a Fuji-Drychem chemical analyzer (Fuji Film, Tokyo, Japan). You have to added the detail Number (eg. 100N, NX10 or other ?). It is important for researchers and we cannot assess the information accuracy. Please re-write and check your paper thoroughly.
5. In material and method of Metabolomic analysis by LSI Medience Co., you wrote the metabolimic analysis. However, we cannot believe LSI Medience Co. can whole metabolome analysis and you have to wrote it correctly (eg. 33 ? Amino acid analysis or Acyl-carnitine analysis etc…).