Author’s response to reviews

Title: Complicated Gitelman syndrome and autoimmune thyroid disease: A case report with a new homozygous mutation in the SLC12A3 gene and literature review

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Author’s response to reviews:

Dear editor

Thank you for your kind letter of “Gitelman syndrome complicated with autoimmune thyroid disease: A case report with a new homozygous mutation in the SLC12A3 gene and literature review” on June 03, 2018. We revised the articles according to the reviewers’ advices, including the main amendments.

1. The title got a slightly change. Many grammatical or typographical errors have been revised.
   We have marked all the changes with yellow highlights.

2. We added some new content to show the whole medical process.
3. Some contents of gene sequence were added.

4. Some discussions have been added, and one references have been added to it.

5. We added some normal range values, and emphasized those came from different medical departments.

The following is the reply to two reviewers, and reviewer's opinion had been marked as blue.

To Katarzyna Ziemnicka, M.D, Ph.D. (Reviewer 2)

Dear Dr. Katarzyna Ziemnicka

I am very grateful to your comments for the manuscript. According with your advice, we amended the relevant part in manuscript. Some of your questions were answered below.

1) The text needs language corrections.

2) and 3). Graves's disease is rather the cause than type of hyperthyroidism. "PH" is not a proper form.

4). There is no information what kind of scale was used to evaluate the muscle strength (references?)

5) Normal ranges for fT3, fT4, TRAB, TgAb and etc. are lacking.
We add the normal range for these data. But it should be attention they were come from another medical department.

6) Thyroglobulin could be elevated in autoimmune thyroid diseases, so in this case doesn't bring in any important information
We delete it as the advice

7) Give the concentration of haemoglobin in more commonly used units (so, g/dl)
This have been corrected as the advice

8) Authors write about leucocytes and neutrophils count, and about CK but there are no detailed data nor in the text or in the tables
We add the data about them

9) The genetic methods should be described more precisely
We have added the method and some other information for sequencing. But limited to the length of the article, we don't have a detailed description about operatioon. If necessary, we can provide a complete genetic testing report.

10) There is no information whether mother and son of proband were homozygous or heterozygous considering mutation in SLC12A3
We have shown that mother and son of patient were heterozygotes in the article.
11, 12) Authors should properly use terms: incidence and prevalence. Gene "variants" should be used instead of gene "variations"

These have been corrected as the advice.

13) Check carefully if all necessary publications were cited and placed in the reference list

We had checked. If you find any problem, please let us know.

14) The titles of the tables should be more accurate and descriptive

Thank you very much for all your help and looking forward to hearing from you soon.

To Marek Saracyn (Reviewer 1)

Dear Dr Marek Saracyn

I am very grateful to your comments for the manuscript. According with your advice, we amended the relevant part in manuscript.

Issue 1, 2, 3, 6, 8: We have changed the title and some text of paper as the advice. The other questions were answered below.

Case: Potassium citrate is not the best choice of treatment, because it can escalate the metabolic alkalosis. Don't you think, the patient needs a radical treatment of GD? Did you plan it? Uncontrolled hyperthyroidism in this patient probably exacerbates the symptoms of GS.

We have tried several potassium supplemen method during hospitalization and found this method can raise blood potassium level to normal. However, the patient didn’t take drug follow
our order after was discharged. We think it was an important reason for the poor effect of potassium supplement. The patient also rejected the treatment of Radioiodine because personal will

Why there is so deep hypothyroidism on the last follow up visit (12thDec)? You did not mention it in the Case section.

In october, patients’s thyroid function had become normal, so we reduced the does of ATD. But patient worry about the recurrence of hyperthyroidism, so he didn’t follow our order, so the thyroid function became declined in december. The thyroid function became normal after patient follow our order. We add some new follow record to show this process. During the course of treatment, the patient showed a great lack of coordination, which occurred many times in his previous treatment for several years. We had mention these in the paper.

Now I will the answer the question about disscusion part.

Is the incidence of GS in Japanese population 10.3/10000 or 10.3/100000?, because further you give all incidence per 100 000? This information will have some influence on the conclusions - the same or 10-fold lower incidence of GS than GD?

About the incidence of GS and GD. We read the literature again, and the data cited is correct. In order to respect the original literature, we decided to use the original data expression. But we modified one “incidence” to “prevalence”. GS used the total prevalence, while GD used the incidence per year, so they are not the same. GD’s incidence will be higher than GS’s.

We mentioned hypothyroidism in the literature review, but we made some modifications at the conclusion to make expression more precise.

In the discussion you should also try to answer for the most interesting question: are there possible join points in the molecular pathogenesis of GS and GD/ATD? I mean, a common
genetic pathomechanisms or at least close chromosomal localization of the GS causative gene (SLC12A3) and possible GD loci (CTLA-4, MHC2, variants of THSR, TG, etc.)

We added some discussion about GD and GS susceptibility genes, but the conclusion was that there is no association between them.

What about the possible links between iodine and potassium metabolism, as you nicely described an iodine and magnesium links?

We had tried to find out more relationship between potassium abnormalities and iodine, but we didn’t find any study about it. Perhaps this is a study blank.

The hypokalemia in your case was really deep. Don't you think, that it can be another reason for such hypokalemic state? I mean, in the discussion section at least you should mention about other possible causes of hypokalemia in your case - channelopathies (defects of CACNA1S, SCN4A, KCNE3) - as a common causes of hypokalemic periodic paralysis.

This is an important part that we neglect in the paper. Thank you for indicated this problem. We have sequenced the elimination of some other hypokalemic diseases, including channelopathies. We added this description to paper. If necessary, we can provide a complete genetic testing report.

Thank you very much for for the kind advice and looking forward to hearing from you soon.

Above is the reply to the reviewer. Thank you and all the reviewers for the kind advice.

Best regards

Sincerely yours Dr luo