Response to Reviewer's comments

Reviewer #1:

1. Title

The authors mentioned in the title that Gitelman syndrome in their case is complicated with acute gastroenteritis. I strongly oppose this statement. Mostly the index case has an incidental gastroenteritis that by chance led to the accidental observation of persistent hypokalemia then further investigations revealed Gitelman syndrome. But there is no evidence that the gastroenteritis is related to Gitelmen syndrome. You mentioned that the patients was previously healthy, she had generalized weakness during the attack of gastroenteritis which is expected. Did this weakness improved after the resolution of gastroenteritis? Then this weakness is not related to the Gitelman syndrome as the authors report. Accordingly, I suggest changing the title of the manuscript to ''Early diagnosis of Gitelman syndrome in a young child; A Taiwanese family study case report''.

Remedy: We thank the reviewer's comment.

During the treatment of acute gastroenteritis, hypokalemia of our index case was accidentally discovered and was the main finding. Some etiologies would induce hypokalemia with metabolic alkalosis, such as profound diarrhea or vomiting, diuretics use, and genetic problems. Vomiting, diarrhea, and generalized weakness improved after her acute gastroenteritis healed, however, her hypokalemia is persistent. Therefore, it alerted us that such hypokalemia might come from other etiology. Acute gastroenteritis complicated our hypokalemia approaching.

The title in our manuscript may give the readers wrong impression, therefore, we will modify our title as suggestion: Early diagnosis of Gitelman syndrome in a young child; A Taiwanese family study case report.

2. Abstract

In the abstract and the manuscript mention that how the disease was accidentally discovered after gastroenteritis.

Remedy: We thank the reviewer's comment. We would like to modify our abstract as below to make it clear.

Line 13-14, Page 2:

However, persistent hypokalemia was observed at the follow-up outpatient department.

3. Introduction

In the introduction, you need to mention Bartter syndrome as the most common differential diagnosis of Gitelman syndrome and it is even more common to present in the age group of your index case.

Remedy: We thank the reviewer's comment. We would like to modify our introduction as below to make it clear.

Line 19-23, Page 3:

However, genetic causes of hypokalemia, such as inherited renal tubular disorders, Bartter's (BS) and Gitelman's (GS) syndromes, are relatively rare, and their diagnosis is challenging especially in children [3]. Most cases of BS are noted in neonates due to polyuria or maternal polyhydramnios, in contrast, the symptom of GS is milder and commonly diagnosed during adulthood[4].

3 Kurtz I. Molecular pathogenesis of Bartter's and Gitelman's syndromes. Kidney Int. 1998: 1396 [PMID: 9767561][10.1046/j.1523-1755.1998.00124.x]
4 Chen H, Ma R, Du H, Liu J, Jin L. Early onset children's Gitelman syndrome with severe hypokalaemia: a case report. BMC Pediatr. 2020: 366 [PMID: 32758191][10.1186/s12887-020-02265-9]

4. **Discussion**

In the discussion, you mentioned that measurement of urinary calcium excretion could help differentiate between Bartter and Gitelman syndrome. Elevated renin and aldosterone in Bartter syndrome is another important differentiating point that should be added. The authors need to clarify some clinical data about their patients.

Remedy: We thank the reviewer's comment.

We would like to modify our discussion as below to make it clear.

Line 29, Page 7 - Line 2, Page 8

Hyperreninemia and hyperaldosteronism may be presented in BS and GS. However, metabolic alkalosis and renin-angiotensin system activation are not obvious in GS, not like BS.

5. Case

Did the patients have any history of salt craving or tetany? Did they have any motor developmental delay? Especially in the young toddler that you mentioned she has generalized weakness. What about their growth parameters? What was their blood pressure? Usually patients with Gitelman syndrome are hypotensive. Did their clinical examination showed chondrocalcinosis, which could be found in these patients?

Remedy: We thank the reviewer's comment.

We would like to modify our manuscript as below to make it clear.

Line 9-11, Page 5:

No history of salt-craving, tetany, motor developmental delay, arthralgia, or arthritis was observed. Her growth parameters and blood pressure were also within the normal range.

6. Figure

It is quit strange that the parents are non-consanguineous as shown in figure 1 and they have 3 affected siblings with an autosomal recessive disease.

Remedy: We thank the reviewer's comment.

We would like to remake our figure and its description. Our case has an amazing extremely low probability!

7. Case

You mentioned that you treated your patients with long-term potassium supplementation. In Gitelman syndrome, magnesium supplementation with either magnesium oxide or magnesium sulfate should be added as well.

Remedy: We thank the reviewer's comment.

We would like to modify our manuscript as below to make it clear.

Line 25-29, Page 6:

These three girls started treatment of oral potassium supplementation (potassium gluconate) and nonsteroidal anti-inflammatory drugs (NSAID) (indomethacin, daily dose of 1 mg/kg/day). Due to gastrointestinal side effects being common (especially diarrhea) and their serum magnesium level was above 1.6 mg/dL, magnesium supplementation was held. Because of the side effects of NSAID and stable condition, their oral medications were shifted to potassium-sparing diuretics (spironolactone) 2 years later.

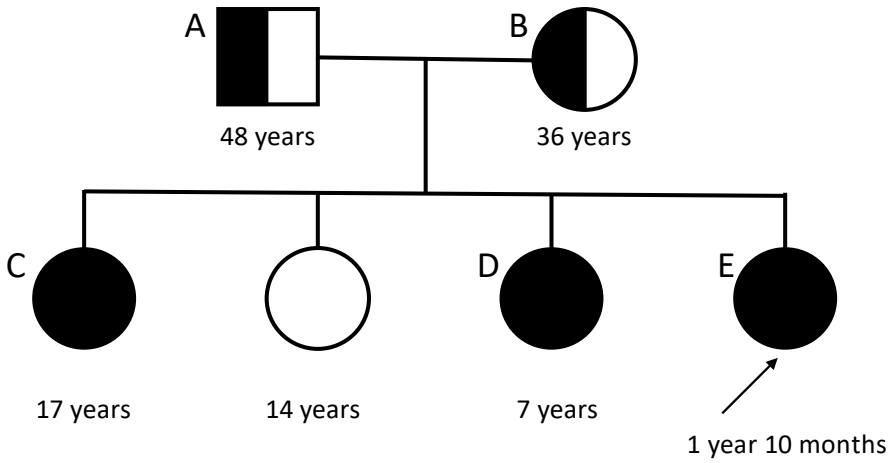
Reviewer #2:

Specific Comments to Authors: It is difficult to understand Figure B. It needs to provide a clear description for the subtitles, or add text to explain it. However, the manuscript is not written very well, it is quite difficult to understand it. In addition, there are many major concerns that need to be addressed by the authors. The clinical case that the authors present in their manuscript is interesting due to the low frequency of this genetic disease and they complement the diagnosis with the family study.

Remedy: We thank the reviewer's comment.

We would like to remake our figure and modify its manuscript as below to make it clear.

(1)



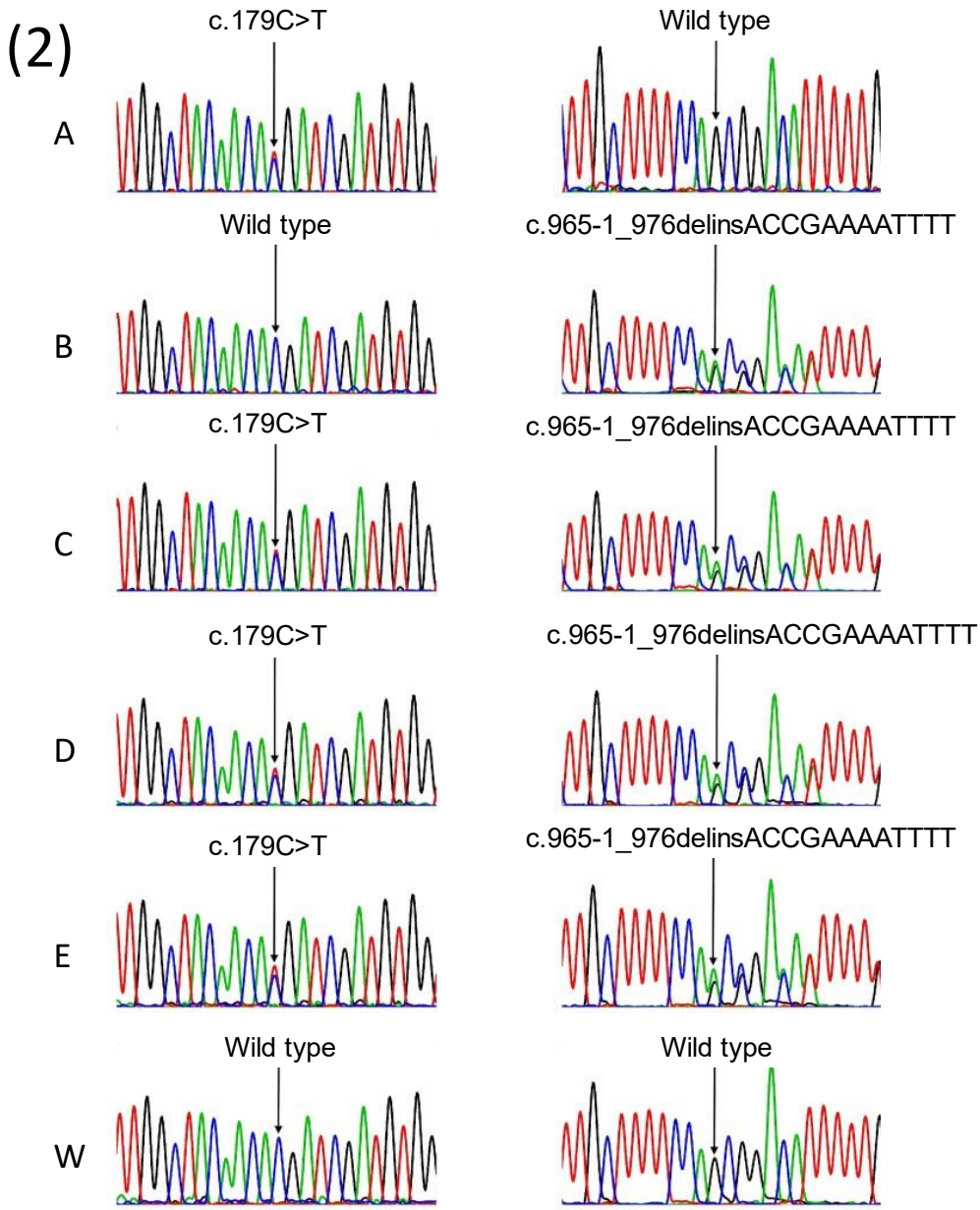


Figure 1. (1) Patient's family tree. (2) Genetic analysis of *SLC12A3* in patient's family. A: Father, a carrier of GS-associated mutations, *SLC12A3*: c.179C>T in exon1. B: Mother, a carrier of GS-associated mutations, c.965-1_976 delins ACCGAAAATTTT in exon8. C: the eldest daughter. D: the third eldest daughter. E: Index patient. W: gene analysis of Wild type. C, D, E revealed compound heterozygous mutations of the gene *SLC12A3*: c.179C>T in exon1 and c.965-1_976delinsACCGAAAATTTT in exon8.

Reviewer #3:

Specific Comments to Authors: The case report is important in cases of rare diseases and facilitates the study and understanding of the pathology for pediatricians and general practitioners. But it's important to mention a few more relevant articles as "Fujimura J, Nozu K, Yamamura T, et al. Clinical and Genetic Characteristics in Patients With Gitelman Syndrome. Kidney Int Rep. 2018;4(1):119-125. Published 2018 Sep 28. doi:10.1016/j.ekir.2018.09.015".

Remedy: We thank this invaluable comment.

This study revealed clinical characteristics, such as the prevalence of complications、developing extrarenal complications, and analyzed the correlation between genotype and phenotype, in GS cases in the Japanese population. We have cited the study as a reference to increase the reliability of our case report.

6 Fujimura J, Nozu K, Yamamura T, Minamikawa S, Nakanishi K, Horinouchi T, Nagano C, Sakakibara N, Nakanishi K, Shima Y, Miyako K, Nozu Y, Morisada N, Nagase H, Ninchoji T, Kaito H, Iijima K. Clinical and Genetic Characteristics in Patients With Gitelman Syndrome. Kidney Int Rep. 2019: 119 [PMID: 30596175][10.1016/j.ekir.2018.09.015]

Reviewer #4:

Specific Comments to Authors: Reviewer Comments and Suggestions for Authors Criteria Checklist for New Manuscript Peer-Review
1 Title. Does the title reflect the main subject/hypothesis of the manuscript? ANSWER: No. I suggest the authors adapt the title, as follows: Gitelman syndrome, diagnosis in an infant: case report and family study.
3 Key words. Do the key words reflect the focus of the manuscript? ANSWER: No. I suggest that the authors delete the term vomiting and add hypomagnesemia.
8 Illustrations and tables. Are the figures, diagrams and tables sufficient, good quality and appropriately illustrative of the paper contents? ANSWER: No. Table 1. I suggest that the authors include in the table only the key laboratory results in the diagnosis and the rest of the values include them in the Case Report section. Figure 1. I suggest that the authors increase the size of the text, it contains text with a very small font. Do figures require labeling with arrows, asterisks etc., better legends? ANSWER: No. Increase the size of some legends, there is text in very small type
11 References. Does the manuscript cite appropriately the latest, important and authoritative references in the introduction and discussion sections? ANSWER: Yes. I only suggest authors to complete the writing of all references, example, Reference 1. Cummings BM, Macklin EA, Yager PH, Sharma A, Noviski N. Potassium abnormalities in a pediatric intensive care unit: frequency and severity. J Intensive Care Med 2014; 29 (5): 269-74. [PMID: 23753253] [10.1177 / 0885066613491708]

Remedy: We thank the reviewer's comment.

We modify our title as below: Early diagnosis of Gitelman syndrome in a young child; A Taiwanese family study case report. We also adjusted the keywords (delete the term "vomiting" and add "hypomagnesemia"). We would like to remake our figure and modify its manuscript as below to make it clear. The references' style was modified as wished.

(1) 70835-Answering Reviewers: Done

(2) 70835-Audio Core Tip: Done

(3) 70835-Conflict-of-Interest Disclosure Form: Done

(4) 70835-Copyright License Agreement: Done

(5) 70835-Approved Grant Application Form(s) or Funding Agency Copy of any Approval Document(s): Done already previously submitted

(6) 70835-Signed Informed Consent Form(s) or Document(s): Done already previously submitted

(7) 70835-Non-Native Speakers of English Editing Certificate: Done already previously submitted

(8) 70835-Video: N/A

(9) 70835-Image File: Done

(10) 70835-Table File: Done

(11) 70835-CARE Checklist–2016: Done

(12) 70835-Supplementary Material: N/A