Peer Review File

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Reviewer A

The authors present a case study of familial hypocalciuric hypercalcemia and affected family members. I suspect the case merits publication but am concerned that in its current form the manuscript will not inform or interest the readership of the journal. A main thrust of the article is that FHH and primary hyperparathyroidism may be difficult to distinguish and that FHH could be considered as an atypical form of primary hyperparathyroidism. The authors also point out that it is important to distinguish between PHPTH and FHH and do not make a convincing case for this classification. At times it seems that they are arguing against themselves. I wonder if they may revise their manuscript to argue more convincingly for either case. They might consider that unlike HPTH the primary lesions occur in many other organs besides the parathyroid. In addition, it may be more helpful for the readership for them to discuss links between pathophysiology and the disease.

Response: The manuscript has been revised with more evidence-based comparison between PHPTH and FHH however, in terms of lesions we did not define any comparisons since it is beyond the scope of this case report as we wanted to draw more focus on biochemical and genetic testing. The pathophysiology of the disease is explained. (Page number 4 and 5 line numbers 72-83 and 85-103).

Why is the heterozygous form of the disease so mild and the homozygous forms so severe? Recently, research has addressed this question and it concerns how the CaSR works as a dimer and how mutant receptors are trafficked by non-mutant receptors (doi.org/10.1371/journal.pone.0266993 and doi: 10.1210/me.2012-1232.)

Response: This information has been added to the manuscript (page number 5 line numbers 109-131)

The authors could achieve this by cutting out parts in which they repeat themselves unnecessarily (for example: "The fact that FHH is an autosomal dominant trait means that it can be helpful to know if it runs in the family. But in about 15%–30% of cases, mutations in the CaSR gene can happen on their own. Negative family history of the disease does not rule it out (8). Similarly, Shinall et al. described that despite its name, FHH is not always a disease that runs in families. The lack of evidence in family screening does not mean that FHH is not present. It is important to note that about a third of individuals with FHH does not have any variations in the CaSR gene (9). However, most of the time it runs in families as Wang et al. reported a case of a 32-year-old man who was diagnosed with FHH and the family survey revealed that all members had hypercalcemia (10). Similarly, Woo et al. presented a case of a family whose 3 members were diagnosed with FHH and thus had CaSR gene mutation (11). This was also true in our case, as our patient's first generation was hypercalcemic" with

"Although FHH is an autosomal dominant disease about 15%–30% of cases may arise due to spontaneous mutations in the CaSR gene (9). The lack of evidence in family screening does not mean that FHH is not present. "
Response: This information has been deleted

Another potential area for strengthening is in the use of citations to support statements. Currently, the first citation in the introduction occurs in the 8th line. Citations could be used before and in many other areas in the manuscript.
Response: More citations have been added accordingly and the manuscript has been revised and updated.

Another idea for potential improvement is to cite definitions for the various subtypes of FHH. This may be useful for the majority of readers.
Response: Types of FHH are added and described. (Page number 2 line numbers 27-31)

Reviewer B

Congratulations on an interesting case presentation. I would recommend a thorough linguistic revision so that your importment scientific message is more clearly and stringently presented.
Good luck!
[Please check the attached marked PDF file for detailed suggestions.]
Response: The manuscript has been revised for better clarity.