Peer Review File

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Reviewer A

This is a well-written manuscript. All important aspects have been addressed. However, there are some issues to be clarified:

We thank the reviewer for the positive comment on our manuscript. The reviewer suggests a set of changes, which tremendously helped us to improve our manuscript. Our specific responses are as follows:

Comment 1: the manuscript does not deliver a clear message. The authors state that approximately 200 pHPT cases have been reported in children and adolescents. What makes this case unique among these 200 reports? Were for example these cases sporadic too? Or syndromic? Why are only 8 cases presented in the table? Are there only 8 cases with hypercalciuric crisis reported in the whole literature? It is totally different if there are 7 or 199 other similar reports.

The authors should find a uniqueness, add a strong statement of purpose at the end of the introduction section and accordingly revise the manuscript to deliver a clear message. From what I have read, I would choose to emphasize the necessity of emergency surgery. It seems to be a very crucial point in the patient's course.

Reply 1:

We are thankful for this comment. As the reviewer pointed out, we have presented eight cases including our case in **Table 1**. We showed these eight cases because they presented hypercalcemic crisis due to PHPT, which is an even rarer condition in pediatric patients. We could not find any other case reports of hypercalcemic crisis caused by PHPT in children with detailed clinicopathological characteristics and clinical courses. We have described this point in Introduction section (Page 3, Line 67-68)

As the reviewer suggested, we modified the introduction section to emphasize the necessity of emergency surgery. We consider that emergency focused parathyroidectomy

prior to genetic testing is an appropriate strategy in pediatric patients with PHPT-induced hypercalcemic crisis (Page 4, Line 69-76).

Changes in the text: Page 3, Line 67-68, and Page 3, Line 69-76

Comment 2: should in children a coexistence of PHPT with FHH be excluded? please, explain.

Reply 2:

We thank the reviewer for this comment. Indeed, we did not exclude PHPT with FHH in our literature research, but there were no reports showing FHH cases which presented PHPT-induced hypercalcemic crisis.

Changes in the text: None

Comment 3: the manuscript has an unacceptably high number of authors. There is no excuse for sixteen authors for a case report of <1500 words, this makes <100 words per author. I encourage the first author to read carefully the ICMJE criteria and accordingly include only co-authors that qualify for authorship. Patient care alone is not enough and does not justify authorship.

Reply 3:

We thank the reviewer for pointing this out. As we referred to the ICMJE criteria, we noticed some authors did not meet the criterion that "drafting the work or revising it critically for important intellectual content", and hence we excluded them from the author list (Page 1, Line 5-6). However, the Editorial office let us know that the line-up of authorship should not be changed at this review stage according to their policy in the decision letter. Hence, we will get contact with the Editorial office regarding this point.

Changes in the text: Page 1, Line 5-6

Reviewer B

In this well written original manuscript, Hayashi et al. report the case of an 11-yo boy who had severe hypercalcemia caused by Primary Hyperparathyroidism (PHPT). Emergency surgery was the only way to have him recover.
I thank the authors for reporting such very rare cases. I have a few comments/ questions.

We would like to really appreciate the reviewer's positive comment. We consider that our manuscript was improved thanks to the reviewer's suggestions. Our specific responses are as follows:

Comment 1: The clinical history is indeed in favor of PHPT (recovery after surgery) but still, it's unusual to see no quantification of calciuria in 2022.

Reply 1:

We thank the reviewer for pointing this out. We have added the data of preoperative calcium level in urine (15.5 mg/dL) in Page 6, Line 116.

Changes in the text: Page 6, Line 116.

Comment 2: The way this boy has been treated (furosemide, pamidronate and calcitonin) should be discussed, regarding the pathophysiological evidences. Bisphosphonates for instance have very weak effects in PHPT (especially because bones very weakly participate to blood calcium level during PHPT, kidneys do most) and, in several developed countries, calcitonin now has been withdrawn. Could cinacalcet be an option? It is in adults awaiting for surgery...

Reply 2:

We thank the reviewer for such an insightful comment. We agreed that bisphosphonate has limited effects if kidney plays a major role in increase of serum calcium level. However, in our patient, as described in Page 5, Line 96-98, his lumber bone mineral density was 0.682 g/cm^2, which was low for his age (normal range for 11-year-old Japanese boy: 0.694–0.706 g/cm^2) (Ref: Nishiyama S et al. Clin Pediatr Endoclinol 2001; 10: 113-20). This indicated that his bone would participate, at least partly, to increase his

serum calcium level. Hence, bisphosphonate can have some effect to decrease serum calcium level in our patient (Page 8, Line 176-178).

Furthermore, in condition of hypercalcemic condition where serum calcium level should be lowered to prevent lethal outcomes, bisphosphonate is an important agent to be used in the initial treatment. Indeed, all six cases of hypercalcemic crisis except for one case (**Table 1**) were treated with bisphosphonate.

As the reviewer pointed out, calcitonin has been withdrawn in some developed countries. However, this agent is currently available for treatment of hypercalcemia in Japan. As in our case where bone is involved in elevation of serum calcium level, we consider that anti-bone resorption agents including a bisphosphonate and a calcitonin can have effect on decreasing serum calcium level (Page 8, Line 177-179).

With regard to other anti-bone resorption agents, cinacalcet, which is currently used to treat secondary hyperparathyroidism and parathyroid carcinoma can be an option even for PHPT in the future (Page 8, Line 179-181).

Changes in the text: Page 5, Line 96-98, and Page 8, Line 176-181.

Comment 3: What was the cause (the pathophysiological one) of the abdominal pain? Did the boy have nephrolithiasis/nephrocalcinosis?

Reply 3:

We are thankful for this comment. Contrast enhanced computed tomography did not show any nephrolithiasis, and we could not find any causes for his abdominal pain from the medical record. However, as previously described, 17% of patients develop abdominal pain among pediatric patients with PHPT (Ref: Fukaya Y et al. Clin Pediatr Endoclinol 2021; 30: 111-113). We assume that he claimed abdominal pain as one of the vague symptoms.

Changes in the text: None

Comment 4: How urgent was the surgery? Was there any cardiac outcome? The story clearly shows that the boy had waited for at least one month before hypercalcemia was found. Was the emergency the abdominal pain? I'm not convinced that lab values alone should indicate emergency surgery.

Line 134: I'm not sure 'it is necessary to lower serum calcium levels as soon as possible to prevent lethal outcomes'. Do we have any evidence for that? I understand that very high calcium values can be scary and are 'at risk'. But I don't know any clinical study that showed that emergency lowering is better than later cautious intervention: usually, to get to such high values, patients developed their condition for months if not for years; in such, they took time to adapt to such high levels; therefore, lowering very quickly their calcium level could lead to serious adverse event. It is exactly what we see in patients with profound hyponatremia and physicians willing to 'correct' it too quickly: they can develop osmotic demyelinating syndrome, and the cure is then worse than the initial disease.

Reply 4:

We appreciate this insightful comment. As the reviewer pointed out, the boy left for more than three months since he had presented the symptoms from hypercalcemia. During this period, hypercalcemic crisis has been developed and he suffered from severe nausea and general fatigue. Due to the severe nausea, he could not take almost any foods when he was transferred to our hospital, and he became lethargic despite of medical treatment. Although he had neither cardiac outcome nor emergency abdominal pain and his serum calcium level decreased to some extent with medical treatments, we decided to perform surgery as soon as possible to improve his symptoms because surgery is the only curative treatment for PHPT (Page 5, Line 104-105, and Page 6, Line 124).

Furthermore, as the reviewer suggested, it remains unknown emergent decrease of serum calcium level is better than later cautious intervention because prospective randomized clinical trial data addressing non-operative management of hypercalcemic crisis is limited (Ref 5: Ahmad S et al. Am J Med 2015; 128: 239-45.). Hence, we have modified the sentences in Page 6, Line 119-120, and Page 8, Line 169-170).

Changes in the text: Page 5, Line 104-105, Page 6, Line 119-120, 124, and Page 8, Line 169-170

Comment 5: Why do the boy still receive alfacalcidol 6 months after surgery? Does he have partial hypoparathyroidism?

Reply 5:

We thank the reviewer for pointing this out. Although the dose of alfacalcidol was gradually decreased from 0.75 μg/day to 0.25 μg/day, he still receives alfacalcidol.

We consider that the remnant parathyroid function is good, as evidenced by maintained intact-PTH level. However, his preoperative lumbar bone mineral density (0.678 g/cm^2), which was low for his age (normal range for 11-year-old Japanese boy: 0.694–0.706 g/cm^2) (Ref: Nishiyama S et al. Clin Pediatr Endoclinol 2001; 10: 113-20). Furthermore, although his serum calcium was maintained within normal limits postoperatively, the calcium level in urine was low. From these findings, we consider that he might be continuously suffered from hungry bone syndrome. Hence, we continued the prescription of alfacalcidol to help recovery from hungry bone syndrome. In fact, his lumbar bone mineral density improved to 0.774 g/cm^2 6 months after surgery, and hence we are planning to stop alfacalcidol treatment in the near future (Page 7, Line 143-144).

Changes in the text: Page 7, Line 143-144

Comment 6: Line 119, authors state they found 'no genetic predisposition' in the family: did they check blood calcium concentrations in the two parents?

Reply 6:

We thank the reviewer for this comment. We did not check the serum calcium levels of his parents, but no genetic predisposition has been identified in this family. We have clarified this point in Page 7, Line 151-152.

Changes in the text: Page 7, Line 151-152.

Reviewer C

Comment 1: Line 47 – what is your age definition of "children"? I am aware that in Japan, adulthood is considered above 20 years old, whereas in most other western countries, the age of adulthood is considered above 18 years old. Also, if this is a case report on a 11 year old, so, instead of using the words "children and adolescents", could substitute for "paediatric"?

Reply 1:

We thank the reviewer for this important suggestion. As the reviewer pointed out, adulthood is above 20 years old in Japan, and hence we included Case 1 (20-year old man) in **Table 1** in the original manuscript. However, in the most of the western countries, adulthood mean above 18 years old. Hence, it would be better that we fixed the definition of children as under 18 years old. Accordingly, we have deleted Case 1 from **Table 1**.

Furthermore, we agreed that we should change the words "children and adolescents" to "pediatric", and have corrected these words throughout the manuscript (Page 1, Line 20-21, Page 2, Line 23-24, Page 3, Line 47-50, 54, 58-60, 66, and 68, Page 4, Line 69-70, 75, and 79, Page 7, Line 160-163, Page 9, Line 196, 204, and 206, Page 10, Line 218, 223-225, and 232, and Page 11, Line 236, 239, 244, and 248-249).

Changes in the text: (Page 1, Line 20-21, Page 2, Line 23-24, Page 3, Line 47-50, 54, 58-60, 66, and 68, Page 4, Line 69-70, 75, and 79, Page 7, Line 160-163, Page 9, Line 196, 204, and 206, Page 10, Line 218, 223-225, and 232, and Page 11, Line 236, 239, 244, and 248-249

Comment 2: Line 55 – hypercalcaemia in adults also causes vague, non specific symptoms, so I don't think these symptoms are uniquely specific to the paediatric population

Reply 2:

We appreciate this comment from the reviewer. We agreed that non-specific symptoms from hypercalcemia is not unique in pediatric patients, and adults with PHPT also can present non-specific symptoms. We have modified this statement (Page 3, Line 56-57).

Changes in the text: Page 3, Line 56-57

Comment 3: Line 63 – this sentence is quite difficult to follow – consider rewording?

Reply 3:

We thank the reviewer for this comment. We are sorry that this sentence was difficult to follow. We consider that PHPT is usually diagnosed before hypercalcemic crisis is developed. That is why PHPT in pediatric patients is likely to be symptomatic, even if the symptoms are vague. We have modified this sentence to be easily followed (Page 3, Line 65-68).

Changes in the text: Page 3, Line 65-68

Comment 4: Line 80 – could rephrase this sentence to "contrast enhanced computerised tomography also demonstrated an enlarged upper right parathyroid gland"

Reply 4:

Thank you for pointing this out. We have changed this sentence as the reviewer suggested (Page 5, Line 92-93).

Changes in the text: Page 5, Line 92-93

Comment 5: Line 84 – instead of "but no", change to "with no"

Reply 5:

We have changed "but no" to "with no" as the reviewer suggested Page 5, Line 95.

Changes in the text: Page 5, Line 95

Comment 6: Line 99 – what is your rationale for looking for and resecting the right paratracheal adipose tissue and the right upper pole of thymus when you have a clearly identified target of the right upper abnormal parathyroid gland? This increases morbidity for the patient, surely?

Reply 6:

Thank you for this comment. We aimed to resect the right inferior normal parathyroid gland in consideration of the possibility of hereditary disease. However, we could not detect the right inferior parathyroid gland. As previously described, inferior parathyroid gland can be located at the upper pole of the thymus (Ref: Reitz R et al. Surgery 2021; 169: 513-518). Hence, we resected the right upper pole of the thymus as well as the right paratracheal adipose tissue (Page 6, Line 126-130). This is because re-operation in the same side as the initial operation would increase the morbidity such as recurrent laryngeal nerve palsy when he develops recurrence of PHPT in the right inferior parathyroid gland.

However, as the reviewer suggested, focused parathyroidectomy to resect the enlarged parathyroid gland would be consequently enough to him. We have discussed this point in Discussion section (Page 10, Line 230-232).

Changes in the text: Page 6, Line 126-130

Comment 7: Line 106 – did the thymus contain a parathyroid gland?

Reply 7:

We thank the reviewer for this comment. The excised thymus did not contain any parathyroid tissue. We have corrected this sentence (Page 6, Line 135-136).

Changes in the text: Page 6, Line 135-136

Comment 8: Line 123 – "treated with emergency parathyroidectomy following failed medical treatment"

Reply 8:

Thank you for this suggestion. We have rephrased this sentence (Page 7, Line 156-157).

Changes in the text: Page 7, Line 156-157

Comment 9: Line 126 – "hypercalcaemic crisis caused by PHPT in children has been considered an even rarer entity"

Reply 9:

We have rephrased this sentence as the reviewer suggested (Page 7, Line 162-163).

Changes in the text: Page 7, Line 162-163

Comment 10: Line 132 – going back to point one – "paediatric" patients in the majority of the western countries are considered below 18 years old, so if you are going to have your age limit at 20 years old, this will need clarifying in the text. Otherwise, lower the limit to 18 years old.

Reply 10:

We appreciate this comment. As described in **Reply 1**, we defined pediatric patients as under 18 years old as in the most of western counties (Page 8, Line 166-167). Accordingly, we have deleted Case 1 from **Table 1**.

Changes in the text: Page 8, Line 166-167

Comment 11: Line 136 – how many patients did you find in the literature review?

Reply 11:

Thank you for this comment and I am sorry for confusing caused by this statement. "All patients" means "All six patients shown in **Table 1**". We have modified the statement in this sentence (Page 8, Line 171)

Changes in the text: Page 8, Line 171

Comment 12: Line 138 – it may be useful to state the denominator of cases (i.e. six out of ? cases = 75%)

Reply 12:

We thank the reviewer for this comment. As the reviewer suggested, we have described as "four out of six cases" (Page 8, Line 173 and 184). On the other hand, **Reviewer E** indicated that the percentage was unnecessary in this section. Hence, we have deleted the percentage.

Changes in the text: Page 8, Line 173 and 184

Comment 13: Line 140 – I would not include your case in the literature review numbers as this will get confusing. Report on the cases from the literature review and then you could do a short summary of your case and how it matches/differs from the literature review

Reply 13:

We appreciate this insightful comment. As the reviewer suggested, we have excluded our own case in these sentences, and described the summary of our case after the literature review (Page 8, Line 176-179).

Changes in the text: Page 8, Line 176-179

Comment 14: Line 143 – why was surgery not performed in this case? I am presuming this is because they were treated medically? Did they have an elective parathyroidectomy once stable? Be useful to include this information if available

Reply 14:

We are thankful for this comment. As the reviewer presumed, Case 6 underwent parathyroidectomy after medical treatments 22 days after admission as described in **Table 1**. Because she had family history of PHPT, genetic testing prior to surgery was performed, and she was diagnosed with HPT-JT as evidenced by a pathogenic mutation in *CDC73* (Page 8, Line 184-186). However, the surgical procedure was focused parathyroidectomy even after genetic testing, and his postoperative course was uneventful. Hence, we still consider that emergency focused parathyroidectomy prior to genetic testing is an appropriate strategy when pediatric patient presents with a hypercalcemic crisis caused by PHPT.

Changes in the text: Page 8, Line 184-186

Comment 15: Line 146 - do you know if the other cases were due to adenomas or due to multiglandular disease? would be interesting to see what sort of surgery was done (targeted/bilateral neck exploration...)

Reply 15:

We thank the reviewer for this comment. As shown in **Table 1**, all the other cases were due to adenoma, which supports the notion that emergency focused parathyroidectomy prior to genetic testing is an appropriate strategy for PHPT-induced hypercalcemic crisis in pediatric patients. We have described this point in Page 10, Line 215-216.

Changes in the text: Page 10, Line 215-216

Comment 16: Line 156 – how can you have a "focused parathyroidectomy with unilateral neck exploration"? is this not just a unilateral neck exploration?

Reply 16:

We appreciate this comment, and are sorry for confusing. Focused parathyroidectomy means that resection of only the enlarged parathyroid gland, while unilateral neck exploration includes the resection of the enlarged parathyroid gland with exploring the other parathyroid gland at the same side.

We consider focused parathyroidectomy as an appropriate treatment to promptly lower the serum calcium level with minimal invasion in pediatric patients with hypercalcemic crisis caused by PHPT. Hence, we have deleted 'with unilateral neck exploration' in this sentence (Page 9, Line 203)

Changes in the text: Page 9, Line 203

Comment 17: Line 160 – again, I would not include your case in the literature review numbers

Reply 17:

We appreciate this comment. As the reviewer suggested, we have excluded the description of our own case in this sentence, and described our case afterwards (Page 9, Line 205-209).

Changes in the text: Page 9, Line 205-209

Comment 18: Line 164 – why did they remove 3 glands?

Reply 18:

Thank you for this query. However, we could not find any reasons from the literature why they removed three glands (Wong P, et al. Postgrad Med J 2001;77:468-70.).

We have deleted this case from **Table 1** because this case is 20-year-old man as described in **Reply 1** and **10** (Page 9, Line 209-211, and Page 10, Line 212).

Changes in the text: Page 9, Line 209-211, and Page 10, Line 212

Comment 19: Line 164 – "in cases 5 and 6"…

Reply 19:

We thank the reviewer for pointing this out. We have corrected this point.

Changes in the text: Page 10, Line 212

Comment 20: Line 173 - I would re-word - you cannot say hypercalcaemic crisis is expected to be less likely based on 60 patients... you could say "hypercalcaemic crisis seems less likely..."

Reply 20:

We thank the reviewer for this insightful comment. As suggested, we have modified this sentence (Page 10, Line 222-223).

Changes in the text: Page 10, Line 222-223

Comment 21: Line 179 – when you say "most", do you have actual figures?

Reply 21:

We thank the reviewer for this important comment. We have modified this sentence (Page 10, Line 228-229).

Changes in the text: Page 10, Line 228-229

Comment 22: Line 182 – please refer to comment on line 156

Reply 22:

Thank you for this comment. We have deleted "with unilateral neck exploration" from this sentence and Page 10, Line 231

Changes in the text: Page 10, Line 231

Comment 23: Line 182 – what is the rationale of unilateral neck exploration when imaging is clearly identifying one overactive gland?

Reply 23:

We are thankful for this comment. As described in **Reply 16**, we consider focused parathyroidectomy, but not unilateral neck exploration as an appropriate treatment to pediatric patient with PHPT-induced hypercalcemic crisis. Hence, we have deleted "with unilateral neck exploration" from this sentence (Page 10, Line 231).

Changes in the text: Page 10, Line 231

Comment 24: Line 193 – you are now saying to just do a "focused parathyroidectomy" and not a unilateral neck exploration….?

Reply 24:

Thank you for pointing this out. As described in **Reply 16** and **23**, we consider "focused parathyroidectomy" but not "focused parathyroidectomy with unilateral exploration" is an appropriate strategy. We are sorry for this confusing.

Changes in the text: None

Comment 25: Line 270 – computer enhanced…

Reply 25:

Thank you for pointing this out. We have corrected this (Page 15, Line 326).

Changes in the text: Page 15, Line 326

Comment 26: Line 273 – use the word "enlarged" rather than "swollen"

Reply 26:

Thank you for this suggestion. We have changed "swollen" to "enlarged" (Page 15, Line 329).

Changes in the text: Page 15, Line 329

Comment 27: Table 1 – consider removal or explaining why you have included Wong et al.'s paper (patient age 20years old)

Reply 27:

We have deleted Case 1 from **Table 1**.

Changes in the text: None

Comment 28: Table 1 – I think it is reasonable to include your case in the table, but not the text

Reply 28:

We appreciate this insightful comment. As the reviewer suggested, we have separately described previously reported cases and our own case in the Discussion section (Page 8, Line 176-186, and Page 9, Line 205-209).

Changes in the text: Page 8, Line 176-186, and Page 9, Line 205-209

Reviewer D

This case is a rare and valuable report. I think it was urgent and difficult, but if possible, please include the following in your report.

We are thankful for the reviewer's positive comment on our manuscript. The reviewer's suggestions led to improve our manuscript. Our specific responses are as follows:

Comment 1: P, Mg, ALP, 25OHD, 1,25(OH)D, calcitonin, PTH-related peptide, glucagon, gastrin, prolactin, ACTH, C-peptide, and IRI values in blood.

Reply 1:

We are thankful for this comment. We have added the following data, phosphorus 1.6 mg/dL (normal range: 3.9–5.8 mg/dL), magnesium 1.4mg/dL (normal range: 1.8–2.3 mg/dL), alkaline phosphatase 325 U/L (normal range: 154–431 U/L), 25-hydroxyvitamin D 25.5 ng/mL (normal range: more than 20.0 ng/mL), 1,25-dihydroxyvitamin D_3 113 pg/mL (normal range: 20–70 pg/mL), calcitonin 3.38 pg/mL (normal range: less than 9.52 pg/mL), PTH-related peptide < 1.0 pmol/L (normal range: less than 1.1 pmol/L), prolactin 2.0 ng/mL (normal range: 3.6–16.3 ng/mL), ACTH 43.4 pg/mL (normal range: 7.2–63.3 pg/mL), and insulin 9.4 μU/mL (normal range: 5.0–25.0 μU/mL) (Page 5, Line 108-115, and Page 6, Line 116). We are sorry that we did not have data of glucagon, gastrin, and C-peptide.

Changes in the text: Page 5, Line 108-115, and Page 6, Line 116

Comment 2: Ca/Cr clearance ratio in urine.

Reply 2:

We have added the data of Ca/Cr clearance ratio in urine (1.67) (Page 6, Line 116-117).

Changes in the text: Page 6, Line 116-117

Comment 3: Values of tubular reabsorption of phosphate and functional excretion of Ca.

Reply 3:

We are thankful for this comment. We have added the information about tubular reabsorption of phosphate (61.0%) and functional excretion of calcium (0.08) (Page 6, Line 117-119). We consider that these values are compatible with PHPT.

Changes in the text: Page 6, Line 117-119

Comment 4: the weight of the removed parathyroid gland, and the size of the parathyroid gland by echo.

Reply 4:

We thank the reviewer for this comment. We have added the information about the weight of removed parathyroid gland (320mg) (Page 6, Line 133-134). We have also added the size of enlarged parathyroid gland measured by ultrasonography (Page 4, Line 90).

Changes in the text: Page 4, Line 90, and Page 6, Line 133-134

Comment 5: the presence or absence of renal stones and bone lesions

Reply 5:

Thank you for this comment. He did not have any renal stones (Page 5, Line 94). Furthermore, his lumber bone mineral density was 0.682 g/cm^2 (Page 5, Line 96-98).

Changes in the text: Page 5, Line 94, and 96-98

Comment 6: the presence or absence of the remaining parathyroid glands swelling at the time of surgery.

Reply 6:

We appreciate this comment. At the surgery, we could not detect the right inferior gland, although we aimed to resect that. On the other hand, we did not explore the parathyroid glands at left side. Preoperative diagnostic imaging tests did not indicate the enlargement of the other parathyroid glands than the removed right superior gland. Altogether, we consider there are no other swelling parathyroid gland than the right superior parathyroid gland (Page 6, Line 126-130).

Changes in the text: Page 6, Line 126-130

Comment 7: In your discussion, please describe the differential diagnosis of this hyperparathyroidism, including family history of this case.

Reply 7:

We thank the reviewer for this comment. We consider that the important differential diagnosis for hypercalcemia in pediatric patients is familial hypocalciuric hypercalcemia (FHH), which shows hypercalcemia with low fractional excretion of calcium (≤ 0.01). In our case, because the fractional excretion of calcium was high as 0.08, FHH was ruled out. We have described this point in Page 11, Line 238-241.

Changes in the text: Page 11, Line 238-241

Reviewer E

This is a valuable description of a rare, but severe, medical occasion: hypercalcemic crisis in a young child. The main focus of the article is to report the case of an 11-year-old boy, treated for hypercalcemic crisis caused by primary hyperparathyroidism. The secondary aim is to conduct a literary review of other reported cases of hypercalcemic crisis in children.

The case description is straight-forward and easily followed and the literary review seems to be adequate, although I have found a few articles that may be included in the material. I have a few minor suggestions listed below.

Thank you for the positive comment on our manuscript. We consider that the reviewer's suggestions helped us to improve our manuscript. Our specific responses are as follows:

Comment 1: (page 2, line 29) "He was immediately started with…" might be rephrased "Treatment was immediately started with…".

Reply 1:

We thank the reviewer for this comment. We have corrected this (Page 2, Line 29-30).

Changes in the text: Page 2, Line 29-30

Comment 2: (page 6, lines 122–133) Consider including following references:
Cronin et a. Primary hyperparathyroidism in childhood and adolescence. J Paediatr Child Health. 1996 Oct;32(5):397-9. Reported a 50% rate of hypercalcemic crisis in their pediatric patient series.
Wang et al. Primary hyperparathyroidism in Chinese children and adolescents: A single-centre experience at Peking Union Medical College Hospital. Clin Endocrinol (Oxf). 2017 Dec;87(6):865-873.

Reply 2:

We agreed that these articles should have been cited in the manuscript. Although we have recognized these articles and aimed to cite in the original manuscript, we could not cite these because there were over 20 citations, which is the limit for Case Report, if we added these. However, we have excluded one article (Wong P, et al. Postgrad Med J 2001;77:468-70.) as suggested by **Reviewer C**. Furthermore, we also deleted one citation (Medina JE, et al. Head Neck 2021.) so that we could cite these two important articles which the reviewer suggested. We have added reference in Page 7, Line 161, and Page 13, Line 306-313.

Changes in the text: Page 7, Line 161, and Page 13, Line 306-313.

Comment 3: (page 6–7, lines 138–141) Percentages unnecessary to report here.

Reply 3:

We are thankful for this comment. As the reviewer indicated, we deleted the percentages (Page 8, Line 173).

Changes in the text: Page 8, Line 173

Comment 4: (page 8, line 164) "In 5 and 6," case 5 and 6? Probably better to summarize as "In two cases, …"

Reply 4:

We thank the reviewer for pointing this out. We have corrected this point. Because we deleted Case 1 from **Table 1** as **Reviewer C** suggested, Case 5 and 6 were changed to Case 4 and 5 (Page 10, Line 212).

Changes in the text: Page 10, Line 212

Comment 5: Would be visually clearer to substitute the y-axes, so that Albumin-corrected calcium is on the right side and intact PTH is on the left since the respective curves are closer to the right respective left. Also, if the reported calcium levels through the article is albumin-corrected, that should be stated both in abstract (page 2 line 29) and case presentation (page 4 line 77).

Reply 5:

We appreciate this insightful comment. As the reviewer suggested, we put albumin-corrected serum calcium on the right side and i-PTH is on the left side in **Figure 2**.

Furthermore, we changed "serum calcium level" to "albumin-corrected serum calcium level" throughout the manuscript (Page 2, Line 28-29, 33-34,36, and 41, Page 4, Line 87-88, Page 5, Line 107, Page 6, Line 123, 132, and, 137-138, Page 7, Line 142, and Page 9, Line 190).

Changes in the text: Page 2, Line 28-29, 33-34,36, and 41, Page 4, Line 87-88, Page 5, Line 107, Page 6, Line 123, 132, and, 137-138, Page 7, Line 142, and Page 9, Line 190

Reviewer F

The manuscript has no novel information, but has several relevant points for discussion that may deserve more attention in the literature. The most important messages needs highlighted and strengthened within the text.

We appreciate the reviewer's suggestions that helped us to improve our manuscript. Our specific responses to the points raised are as follows:

Comment 1: Brief mentioning of the concentrations of vitamin D, magnesium, phosphate and alkaline phosphatase is reasonable.

Reply 1:

We thank the reviewer's comment. We have added the data of vitamin D, magnesium, phosphate and alkaline phosphatase. Serum phosphorus level was low (1.6 mg/dL) (normal range: 3.9–5.8 mg/dL), meanwhile 1,25-dihydroxyvitamin D_3 113 pg/mL (normal range: 20–70 pg/mL) was high. Magnesium, alkaline phosphatase, and 25-hydroxyvitamin D were within normal limits as 1.4mg/dL (normal range: 1.8–2.3 mg/dL), 325 U/L (normal range: 154–431 U/L), and 25.5 ng/mL (normal range: more than 20.0 ng/mL), respectively.

We also added the information of phosphorus, calcitonin, PTH-related peptide, prolactin, ACTH, and IRI as **Reviewer D** suggested. (Page 5, Line 108-115, and Page 6, Line 116)

Changes in the text: Page 5, Line 108-115, and Page 6, Line 116

Comment 2: L49-58: the case illustrates that hypercalcemia in childhood is difficult to diagnose (in in hospital) due to unspecific symptoms and its rarity. This should be more clear in this section.

Reply 2:

We are thankful for this comment. As **Reviewer C** suggested in **Comment 2**, non-specific symptoms from hypercalcemia are not unique in pediatric patients, but adults with PHPT also can present non-specific symptoms. Accordingly, we have modified this

section. We consider that the difficulty of early PHPT diagnosis in pediatric practice is attribute to the rarity of PHPT in pediatric patients and non-specific symptoms of PHPT (Page 3, Line 58-60).

Changes in the text: Page 3, Line 58-60

Comment 3: L71-2: Did the child not have other symptoms - polyuria, lethargy, weight loss? Your opportunity to teach the reader about symptomatic hypercalcemia.

Reply 3:

Thank you for this important comment. We could not find any history of polyurea and weight loss from his medical record. On the other hand, he became lethargic despite of medical treatment. We described this point in Page 5, Line 104-105

Changes in the text: Page 5, Line 104-105

Comment 4: L 77: intact PTH of 405?

Reply 4:

Thank you for pointing this out. We have corrected this sentence (Page 4, Line 87-89).

Changes in the text: Page 4, Line 87-89

Comment 5: L89: hypercalcemic crisis - previously (L61-63) described to have multiorgan involvement and with a risk of being fatal - please elaborate on your patient's presentation

Reply 5:

We appreciate this comment. Our case was diagnosed as hypercalcemic crisis with highly elevated albumin-corrected serum calcium level (18.0 mg/dL) and associated severe nausea. However, emergency surgery following medical treatments to lower

calcium level prevented a fatal consequence. We have described this point in Page 9, Line 189-192.

Changes in the text: Page 9, Line 189-192.

Comment 6: L 93: only single dose of pamidronate?

Reply 6:

Thank you for pointing this out. Only single dose of pamidronate (30mg) was administered. We have clarified this point (Page 6, Line 120).

Changes in the text: Page 6, Line 120

Comment 7: L 109: some cases in the literature are treated with alfa-calcidol like this one, others are not. This would be an interesting point for brief discussion. Rationale (opposed to calcium supplements)?

Reply 7:

We are thankful for the reviewer's suggestion. Alfacalcidol have been widely used in the treatment of a variety of metabolic bone diseases, such as rickets/osteomalacia, renal osteodystrophy, and osteoporosis (Reichel H, et al. N Engl J Med 1989 13;320:980-91) because it can help calcium absorption from gastrointestinal tract.

In our patient, his preoperative lumbar bone mineral density was low (0.678 g/cm^2) (normal range for 11-year-old Japanese boy: 0.694–0.706 g/cm^2) (Ref: Nishiyama S et al. Clin Pediatr Endoclinol 2001; 10: 113-20), which indicated that PHPT induced bone resorption. Hence, we consider that alfacalcidol can help his bone osteogenesis after the surgery. In fact, his lumbar bone mineral density improved to 0.774 g/cm^2 6 months after surgery, and hence we are planning to stop alfacalcidol treatment in near future (Page 7, Line 143-144).

However, the previous reports in which alfacalcidol was prescribed (Ref 7: Choudhry KS, et al. Lupus 2013;22:847-50, Ref 8: Mamedova, et al. Horm Res Paediatr 2020;93:272-8, Ref 10: Sala TD, et al. J Crit Care Med (Targu Mures) 2019;5:34-9, Ref

11: Walczyk A, et al. Endokrynol Pol 2011;62:346-50.) provide neither the detail information about bone mineral density nor the reasons for administration of alfacalcidol. Hence, we could not know why alfacalcidol was used after the surgery.

Changes in the text: Page 7, Line 143-144

Comment 8: L123-6: incidence may not be a representative measure as this condition is very rare

Reply 8:

We thank this insightful comment. We agreed that incidence would not be a representative measure for PHPT-induced hypercalcemic crisis that is not frequent condition. We have deleted this sentence and stated that "Previous reports showed that PHPT rarely developed hypercalcemic crisis in pediatric patients." (Ref 2: Mallet E. Horm Res 2008;69:180-8, Ref 14: Sharanappa V, et al. World J Surg 2021;45:488-95, Ref 13: Cronin CS, et al. J Paediatr Child Health 1996;32:397-9, Ref 15: Wang W, et al. Clin Endocrinol (Oxf) 2017;87:865-73.) (Page 7, Line 160-161)

Changes in the text: Page 7, Line 160-161

Comment 9: L182-3: parathyroid adenoma: prolonged increments of PTH may stimulate and thus increase the size of an adenoma

Reply 9:

We thank the reviewer's comment. The previous report showed that large parathyroid adenomas are more likely with higher PTH level (Filser B, et al. Langenbecks Arch Surg 2021;406:1607-1614), which suggest that prolonged increments of i-PTH may facilitate the enlargement of parathyroid gland. In our case, the removal parathyroid was 15 × 10 mm in size (Page 6, Line 134).

Changes in the text: Page 6, Line 134

Comment 10: L184-9: Integrate in previous sections

Reply 10:

Thank you for this suggestion. We have integrated these two paragraphs (Page 10, Line 217-235, and Page 11, Line 236-241).

Changes in the text: Page 10, Line 217-235, and Page 11, Line 236-241

Comment 11: L 194: prior to genetic testing

Reply 11:

We thank the reviewer for pointing this out. We have corrected (Page 11, Line 246).

Changes in the text: Page 11, Line 246

Reviewer G

This is a well written case report of a hypercalcemic crisis in an 11 year old boy. The authors found only 7 other cases reported in the literature. It should be of interest to parathyroid surgeons. There is a nice discussion of the management strategies and the figures are informative..

We thank the reviewer for the positive comment on our manuscript.