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Hypercalcemia- An enigmatic cause of acute pancreatitis

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Handeling editor:
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1st Editorial decision
04-Apr-2022

Ref.: Ms. No. JCTRes-D-22-00030
Hypercalcemia- An enigmatic cause of acute pancreatitis
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Dear Dr Tiwari,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by May 04, 2022.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

EDITOR:

Please present as case series instead of original research.

Reviewer #1: This manuscript reports on the causes of acute pancreatitis over a year and describes 3 cases (3% of the causes) which were related to hypercalcemia (a multiple myeloma, a parathyroid adenoma and vitamin D toxicity)

This manuscript is interesting since epidemiological analysis of the causes of pancreatitis is rare.

Nevertheless, the manuscript is more a case series than an original research.

- The undetermined causes could correspond to genetic hereditary pancreatitis. Was a genetic study performed?

- The third case, vitamin D intoxication, could correspond to a genetic abnormality of vitamin D catabolism such as CYP24A1 mutations (but other genes may be involved). Were eyedrops which sometimes contain vitamin D, searched in the list of medications?

Hyperparathyroidism complicating CYP 24A1 mutations. Loyer C, Leroy C, Molin A, Odou MF, Huglo D, Lion G, Ernst O, Hoffmann M, Porchet N, Carnaille B, Pattou F, Kottler ML, Vantyghem MC.Ann Endocrinol (Paris). 2016 Oct;77(5):615-619.

- The reference list should include other studies on the same topic

- the corrected blood calcium levels of the other cases of pancreatitis should have been reported if available

Reviewer #2: This is an interesting summary of three cases however hypercalcaemia as a cause of AP has been well described.
It would be helpful to present these cases in the context of what is already known eg what % of AP causes by hypercalcaemia is due to each of the 3 pathologies- certainly I would think hypercalcaemia due to thyrotoxicosis is rare.
For case 2 a more complete work of hypercalcaemia including a consideration of FHH would be beneficial and a more comprehensive discussion of the management of AP in hypercalcaemia -eg strategies to acutely lower calcium, if they are needed etc.

Authors' response

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Varanasi, April 8, 2022

Re: Revision JCTRes-D-22-00030

Dear Dr Michal Heger,

Thank you for providing us an opportunity to resubmit a revised version of our manuscript entitled 'Hypercalcemia-An enigmatic cause of acute pancreatitis.'

We have addressed all comments of both reviewers. Every modification or rebuttal of the reviewer's comment is detailed per comment in red. We are grateful for the useful comments from the reviewers as a result of which our manuscript has been improved a lot. Any change in manuscript and references has been highlighted in yellow.

Thank you again.

On behalf of the authors, kind regards.

Anurag Kumar Tiwari

Reviewer's comments and reply

Editor #: To present as case series instead of original research.

Response: Article has been changed to case series in methods section. Changes highlighted in yellow. During submission option of case series is not available in drop down list, hence original article selected.

Reviewer #1

Query1: The undetermined causes could correspond to genetic hereditary pancreatitis. Was a genetic study performed?

Answer: No, genetic study was not performed for hereditary pancreatitis. Same has been mentioned in methods section.

Query2:The third case, vitamin D intoxication could correspond to a genetic abnormality of vitamin D catabolism such as CYP24A1 mutations (but other genes may be involved). Were eye drops which sometimes contain vitamin D, searched in the list of medications?

Answer: No, patient was not taking any sort of medication prior to onset of pancreatitis. Search for use of eye drop use made telephonically with patient and she denied any such use. Same has been incorporated in discussion section of manuscript. However, genetic analysis including CYP24A1 as suggested was not performed which could have helped in finding the cause of hypervitaminosis D.

Relevant text modified in discussion section.

Query3: The reference list should include other studies on the same topic?

Answer: Relevant studies with references included in the Manuscript. Changes highlighted in yellow.

Following text included in manuscript.

Introduction:

"Usual causes of hypercalcemia include hyperparathyroidism (PHPT), malignancies including multiple myeloma, vitamin D toxicity, sarcoidosis, familial hypocalciuric hypercalcemia (FHH) and total parenteral nutrition.

Acinar cells of pancreas are initiating site of pancreatic injury. Hypercalcemia induced pancreatitis may be calcium sensing receptor (CaSR) dependent or independent however exact mechanism still to be elucidated. Raised intracellular calcium activates calcineurin leading to intracellular activation of pancreatic enzymes (e.g. trypsin) and activation of NF-kb resulting in pancreatic injury and systemic inflammatory response syndrome (SIRS)."

Discussion:

"Hypercalcemia has been reported to be causative in 1.5-8 % cases of AP and majority occurs in setting of hyperparathyroidism."

Query4: The corrected blood calcium levels of the other cases of pancreatitis should have been reported if available

Answer: Calcium levels of all patients (corrected for albumin) and ionized calcium in selected patients are available and are either within normal range or lower except in these 3 reported cases.

Relevant text included in methods section.

Reviewer# 2

Query 1: what % of AP caused by hypercalcemia is due to each of three pathologies?

Answer: Following text included in manuscript in discussion section.

"Hypercalcemia has been reported to be causative in 1.5-8 % cases of AP and majority occurs in setting of hyperparathyroidism. Although approximately 21% of newly diagnosed symptomatic myeloma patients show elevated serum calcium levels, reported cases of acute *pancreatitis* in patients with *multiple myeloma* is surprisingly rare. PHPT has been associated with AP, RAP and CP and overall frequency of pancreatitis in PHPT ranges between 3-13 %. Prevalence of hypercalcemia in hyperthyroidism may be up to 20%, but usually mild and severe hypercalcemia leading to symptoms is rare. Exact frequency of pancreatitis in setting of hypervitaminosis D and hyperthyroidism could not be found in literature as most reports are in the form of case reports. We found 1 patient of AP each resulting from multiple myeloma, hyperparathyroidism and hypervitaminosis D/hyperthyroidism respectively. But it could not be ascertained in 3rd case if hypercalcemia was due to hypervitaminosis D or hyperthyroidism. More so the cause of hypervitaminosis D could not be found, however genetic causes of HVD were not ruled out."

Based on this study hypercalcemia was causative in 3 % patients of AP and 1% each resulted from multiple myeloma, hyperparathyroidism, and HVD/hyperthyroidism.

Query 2: For case 2 a more complete work up of hypercalcemia including a consideration of FHH would be beneficial and a more comprehensive discussion of the management of AP in hypercalcemia-e.g. strategies to acutely lower calcium, if they are needed etc?

Answer: **Complete work up to rule out Familial hypocalciuric hypercalcemia was not done in 2nd case and following points has been added to manuscript in discussion section.**

"Etiology of hypercalcemia in case 2 was evaluated with findings of raised iPTH and low serum vitamin D3 level. Imaging of her neck revealed a solid hypoechoic 2.7 centimeters lesion with lobulated irregular margins posterior to left lobe of thyroid gland (parathyroid adenoma). These findings suggested PTH dependent hypercalcemia. However, 24 hour urinary calcium and urine calcium to creatinine ratio was not measured in evaluation of FHH. FHH is a rare autosomal dominant condition resulting from mutation in calcium-sensing receptor (CaSR) gene causing decreased receptor activity. It is very difficult to distinguish FHH from PHPT in absence of a family history of hypercalcemia. Obtaining serum calcium levels from 1st degree relatives of patient would have been beneficial in this regard, however it was not done. Genetic analysis for CaSR gene mutation was also not performed in this case. Finding a solitary adenoma in patient with FHH has been reported and this fact further complicated the distinction between FHH and PHPT, however our patient responded well to removal of her parathyroid adenoma during 2 months follow up which favors final diagnosis of PHPT due to parathyroid adenoma as FHH patients usually do not respond to sub-total parathyroidectomy or removal of adenoma."

Management of hypercalcemia- Strategies to acutely lower serum calcium level-

Following text has been included in manuscript in discussion section-

"Treatment approaches like rapid hydration, calcitonin spray, corticosteroids etc are used to acutely lower the serum calcium levels in cases of severe hypercalcemia (serum calcium levels >14mg/dL) to prevent or treat episodes of cardiac arrhythmia.

Calcium levels in our all 3 patients were less than 14 mg/dL suggesting moderate hypercalcemia where acute lowering of serum calcium is not required usually, however all patients were given adequate intravenous fluid as required in case of acute pancreatitis and were monitored regularly with serial calcium measurement and electrocardiogram for arrhythmia."

2nd Editorial decision
08-Apr-2022

Ref.: Ms. No. JCTRes-D-22-00030R1
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Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers: