Author’s response to reviews

Title: Sodium valproate induced acute pancreatitis in a bipolar disorder patient: a case report

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Author’s response to reviews:

Dear Editor and Reviewers,
Thank you for your mail and for the reviewers’ comments concerning our manuscript entitled “Sodium valproate induced acute pancreatitis in a bipolar disorder patient: a case report” (manuscript number: PHAT-D-18-00290R1). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our case. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked red in the paper. The main corrections in the paper and the responds to the reviewers’ comments are as followed:

Response to the reviewer’s comments:
Jiraganya Bhongsatiern, PhD (Reviewer 1):
1. Response to comment: how did we rule out comediations such as quetiapine and lithium carbonate?

The first reason is that the patient only presented with acute pancreatitis after receiving VPA. Chang et al. have reported that a 58-year-old man diagnosed with schizophrenia for 20 years exhibited two episodes of acute pancreatitis. The first episode was during comedication of quetiapine and VPA, whereas the second episode was quetiapine alone. The patient in Chang’s report had received quetiapine plus VPA for 10 years, while VPA had been prescribed to our patient for only 1 year. Before VPA treatment, the patient received quetiapine and lithium carbonate, without the symptom of acute pancreatitis.

Second, VPA has been reported as a Class I medication associated with acute pancreatitis. We agree with the Reviewer that quetiapine is related to acute pancreatitis in few cases. Based on the published case reports, there is lacking of clinical data to support whether VPA- and quetiapine-induced acute pancreatitis share similar symptoms. According to the previously published findings, the symptoms may be relatively similar. However, we have little evidence to distinguish VPA-induced pancreatitis from quetiapine-induced pancreatitis. Additionally, there is limited existing evidence to support the assumption that quetiapine combines with VPA to react in the pathogenesis of the disease. Some data on lithium carbonate and pancreatitis can be obtained from a number of sources including the Food and Drug Administration, and ehealthme...
It has been reported that female patients (40-49 years old) who received lithium carbonate for 1-6 months have a higher risk of developing pancreatitis. But still, there is no compelling evidence that lithium carbonate is associated with the risk of pancreatitis. Therefore, we speculated that VPA may be the underlying cause of acute pancreatitis in this case.

Furthermore, the results of follow-up somehow proved our hypothesis that VPA is the exact cause of acute pancreatitis. We have followed up the patient several times before writing this case report. He has maintained a stable mood and no signs of acute pancreatitis recurrence, under the treatment of quetiapine (800 mg/day) and lithium carbonate (1.0 g/day). In addition, the patient regularly examined blood amylase levels after discharging from our institution, and the results were all within the normal range. Taken altogether, our findings indicate that VPA is the most possible cause of acute pancreatitis in this case. We have made correction for this part (Discussion and conclusion, line 9-18, page 9).

2. Response to comment: what was the normal range for amylase, lipase and blood fat?
The normal ranges for amylase and blood lipids were now added in the manuscript (Case presentation, line 26-28, page 7). However, all the biochemical laboratories of the three institutions did not perform lipase testing, and only the blood test results obtained from the first hospital demonstrated that the levels of free fatty acids were normal (range: 0.10-0.90 mmol/L). Besides, the patient’s amylase level returned to normal shortly after stopping VPA treatment. However, its level increased again a few days prior to hospital discharge. A previous study by Balen and Genton (2000) has suggested that elevated amylase levels can be observed in patients receiving VPA therapy, but this does not indicate the recurrence of acute pancreatitis. During the follow-up period, he remained symptom-free after treated with quetiapine (800 mg/day) and lithium carbonate (1.0 g/day). We have made correction for this part (Case presentation, line 49-50, page 7).

3. Response to comment: this report is not scientific enough.
First of all, we apologize for our inappropriate writing, and have made correction according to the reviewer’s comments by using reputable English language editing service. Before the patient suffered from acute pancreatitis, he has prescribed VPA for 1 year. Hence, the two admission dates with the first one indeed was not the date that VPA was started. Throughout the course of treatment, the patient has been continuously treated with quetiapine, lithium carbonate and VPA before we assumed that VPA is the cause of acute pancreatitis (Case presentation, line 19-20, page 7). After withdrawing VPA treatment, we increased the dose of lithium carbonate to 1.0 g per day, instead of switching the mood stabilizer (Case presentation, line 40-44, page 7).

Georgios D. Kotzialidis (Reviewer 2):
Response to comment: First, we sincerely apologize for our negligence in writing this report. According to your valuable suggestions, our manuscript has now been edited by a professional language editing service in order to improve the quality of written English. The abstract section strictly followed the editorial formatting guidelines, but we have rewritten some parts to make it more concise. Moreover, the words ‘Japanese authors’ have been removed, and the article has been cited accordingly (Background, line 36-39, page 6). Indeed, we did not switch the mood stabilizer but increased the dose of lithium carbonate to 1.0 g per day after withdrawing VPA treatment (Case presentation, line 40-44, page 7). Once again, we apologize for being
unscientific when translating our manuscript, and hope the correction will meet your approval. Thank you.

Janet Mifsud de Gray, Phd (Reviewer 3):
Response to comment: Considering the given comments and suggestions, we have again contacted the patient’s sister a few days ago. According to his sister's statements, their family members have no history of bipolar disorder or similar adverse reaction to medications. The patient recheck amylase levels several times after discharging from our institution, and the results were all normal. In addition, he is now receiving quetiapine (800 mg per day) and lithium carbonate (1.0 g per day) as bipolar disorder treatments, and has returned to work as postman. Last but not least, we truly apologize for all the spelling mistakes and grammatical errors, and have revised the manuscript accordingly. Thank you so much.

We tried our best to improve the manuscript and made some changes in it. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in red in revised paper. We appreciate for Editors and Reviewers’ warm work earnestly, and hope that the correction will meet with approval. Once again, thank you very much for the comments and suggestions.