**Author’s response to reviews**

**Title:** Hyperglycemia-related central pontine demyelinization after a binge-eating attack in a patient with type-2 diabetes: a case report

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Reviewer 1):

The article is well written and informative. The more appropriate word would be "Serum Ammonia levels" rather than serum ammonium and may be replaced.

Answer: The changes were made accordingly.

The similar article has already been published recently: Sharma C, Kumawat BL, Panchal M,B et al. BMJ Case Rep 2017. doi:10.1136/bcr-2016-219148

Please read the article and cite ,add relevant points in discussion.

Answer: This article was cited in the discussion with regard to acute versus subacute hyperglycemic events (Discussion and Conclusion, page 7, first paragraph, last sentence):
“The mild hyponatremia on admission is regarded as a pseudohyponatremia due to the concomitant hyperglycemia and has been seen in similar case in an acute setting [4], however, not in a subacute setting as shown in a case of a type-1-diabetic, non-ketoacidotic patient who temporarily stopped insulin treatment [9].”

In addition, the reference was cited in the Background (Page 3, Line 7-8): “...in type-1 diabetes [9].”

Reviewer 2): Pliquett and colleagues submit for review a report of a case of central pontine myelinolysis that occurred in the setting of severe hyperglycemia and in the absence of significant sodium shifts. The report is valuable in that it replicates the findings of other similar reports and has the potential to make an even stronger case than previous reports that hyperglycemia is the culprit. The following are suggestions for improving the current manuscript draft:

1. The case on a clinical basis for CPM should be better made and illustrated by providing a more detailed neurologic exam, especially at admission, peak severity, and discharge, and follow-up. The information provided in the current draft does not demonstrate to the reader the clinical picture nearly well enough.

Answer: Thank you for this very important point.

The neurological assessment has been carefully revised. The course of events was clarified in the manuscript.

Page 2, abstract, 5th line: ”...was admitted due to dysmetria...” (deleted: “paresis”).

Page 3, case presentation, 1st-5th line: ”...was admitted as an emergency due to a suddenly occurring dysmetria, a lack of coordination of his of his right arm, weakness and difficulty to speak since 5 days prior to hospitalization. In addition, gait disturbance, dizziness and vertigo with tendency to fall to the right side, and an intractable pain in both legs occurred one day prior to hospitalization.”

Page 3, case presentation, 6th -7th line: "On admission, the level of consciousness appeared to be normal.”
Page 5, case presentation, 2nd paragraph: “A neurological exam was performed on the 9th day in hospital when the neurocognitive performance and the level of consciousness suddenly decreased. No paresis was found. Strumpell’s sign was positive, Babinski’s sign was negative. In addition, dysarthria, signs of dysmetria including dysdiadochokinesis (both sides) and an ataxia both at rest and when walking were found. On the next day, the patient was somnolent. However, the level of consciousness gradually improved by the 15th day in hospital.”

Page 7, discussion and conclusion, 2nd paragraph: “Interestingly, on admission, the level of consciousness appeared to be normal, a paresis was not found. Therefore, an urgent neurological exam was not mandated. The dysmetria of his right arm, the gait disturbance, dizziness, and vertigo were attributed to the hepatic encephalopathy first. By the 10th day in hospital or 16th day after glucose ingestion, both the coordination disturbances and the level of consciousness deteriorated, even though serum ammonia levels were lower. In absence of any other explanation, these neurological symptoms are attributed to the central pontine myelinolysis.”

2. The MRI data would be better if the ADC maps were shown to demonstrate true restricted diffusion.

Answer: As MRI was gathered shortly before admission in an outpatient clinic, the authors are unable to provide the ADC maps as requested. Therefore, this suggestion cannot be incorporated into the manuscript.

3. The case for hyperglycemia-mediated increased in serum osmolality should be made as strongly as possibly. Can the authors calculate serum osmolality (or use the measured value) over the admission and plot it against time in a single graph that also does the same for the serum sodium and glucose concentrations? The rate of rise of the serum sodium concentration is especially important to show. Incorporation of pre-admission data that shows definitive sudden increase in serum osmolality around the time of symptom onset (or preceding by a few days to a week) would be very interesting if the data are available as it would be conclusive proof that a sudden rise in serum osmolality due to glucose and not sodium is the culprit. Graphing these data would be much more useful than what the authors show, which is an expected decrease in serum glucose concentration during the hospital admission.
Thank you for this great comment. The Figure 1 was redrawn accordingly. During hospitalisation, average daily glucose, sodium, urea and calculated osmolality are graphed there. However, the only valuable data (incorporated in Figure 1) is pre-hospital glucose at five days prior to admission, or one day after glucose ingestion, respectively. Other pre-hospital laboratory data were not determined.

4. If the level of consciousness was indeed normal at discharge, and he was just encephalopathic, how do the authors explain this? The pontine lesion would not necessarily be expected to cause this. Was there more widespread osmotic myelinolysis, such as in the corpus callosum? Other explanations?

Answer: These considerations and possible other explanations were included in the discussion and conclusion: Page 7, 3rd paragraph:

“Hypothetically, osmotic myelinolysis may have been more widespread, i.e. not being restricted to the pons, thereby accounting for the impairment of consciousness in this case. The detailed mechanism, why symptoms are lagging behind the pathophysiological cue “hyperglycemia”, is unclear. Most likely, underlying conditions such as liver cirrhosis and encephalopathy may predispose to central pontine myelinolysis [10], and affect the course of disease.”

5. Cirrhosis was probably a risk factor for the development of CPM in this patient. While his glucose intake preceding admission was quite dramatic, I suspect that it was the combination of this plus cirrhosis that led to CPM -- many other patients have probably had similar sugar ingestion binges without CPM. The authors should discuss this in the discussion section.

Answer: True. These considerations were included in the discussion and conclusion, Page 8, first paragraph: “A decompensated liver cirrhosis may lead to shifts of water, when ascites is present. In addition, in cases of massive glucose ingestion, the liver capacity for glucose disposal may be limited. Hypothetically, self-control, psychological inhibition to cues may be reduced in alcoholic Korsakoff’s Syndrome most likely due to structural or functional changes in the prefrontal cortex [11].“
6. The conclusion, both in the abstract and body should emphasize that the case demonstrates that CPM can be caused by sudden, severe, and sustained hyperglycemia, especially when another risk factor (in this case, cirrhosis) is present. This is the real value of the case. There are plenty of other, better reasons for diabetic patients to modify their sugar intake and adhere to prescribed insulin regimens.

Answer: Thanks. Changes were made accordingly:

Abstract, Page 2, last 5 lines: “Central pontine and/or cerebellar myelinolysis can be caused by sudden, severe, and sustained hyperglycemia, especially when another risk factor (in this case, liver cirrhosis) is present. Functional neurological deficits in the context of hyperglycemia should prompt for the consideration of this differential diagnosis in all diabetes patients.”

Discussion and Conclusions, Page 8, last 7 lines:

„Thus, this case shows that central pontine and/or cerebellar myelinolysis can be caused by sudden, severe, and sustained hyperglycemia, especially when another risk factor (in this case, liver cirrhosis) is present. New-onset, functional neurological deficits in the context of hyperglycemia should prompt for the consideration of this differential diagnosis. Clearly, in all diabetes patients, diabetes counseling and the control of insulin therapy, once initiated, are basic measures to prevent hyperglycemia-related complications such as central pontine myelinolysis.”