Title: Extrapontine myelinolysis associated with pituitrin: case report and literature review

Authors:

Liying Zhuang (zhuangliying43205409@126.com)
Ziqi Xu (ziqi2458@163.com)
Yaguo Li (tiglyq@163.com)
Benyan Luo (luobenyan@zju.edu.cn)

Version: 4  Date: 11 September 2014

Author's response to reviews: see over
Dear editors in chief and peer reviewers,

Firstly, we want to express our sincere thanks for all that you have done for our work. Your objective, thoughtful, detailed and constructive comments are of great help for us to improve the manuscript better.

Secondly, we will provide a detailed description of the revisions in the version of the manuscript as follows: A) The comments of the two reviewers were mainly on the "case presentation" section, during which some details were not clear enough, and on the "conclusions" section, during which some interpretation was not well balanced. Based on those, we have searched for the relative citations, read through the articles seriously and have improved the "case presentation" and "conclusions" sections, with the "references" part revised accordingly. B) There have been some minor points in the quality of the written English, so the manuscript has been further edited by American Journal Experts (http://www.journalexperts.com/cn/about-us).

You will be able to see all of our changes using the Track Changes feature of Microsoft Word when you open the manuscript file.

Thirdly, the detailed responses to the reviewers are displayed below, highlighted with each reviewer.

At last, thank you again, and we are looking forward to your final acceptance of the revised manuscript and publication in the BMC Neurology.

We would like to be contacted by you without any hesitate.

With the best wishes!

Yours sincerely,

Liying Zhuang and Benyan Luo

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Responses to reviewer Aaron de Souza:

Thank you so much for your detailed and constructive comments (covering the aspects of biochemical tests, clinical symptoms, treatments and conclusions) which are of great help for us to revise the manuscript better.

1. Were any biochemical tests done to define the mechanism of hyponatraemia in the patient reported? Was the patient euvolaemic, dehydrated or hypervolaemic? What treatment was given: 0.9% saline, hypertonic saline, oral salt, or volume repletion?

R: Thank you so much for your thoughtful questions. 1) Biochemical tests were done as follows: liver and renal function normal, serum osmolality 253mOsm/kg H2O, thyroid function normal, serum cortisol and adrenocorticotropic hormone were within normal range. So, it was hypotonic hyponatremia based on serum osmolality. 2) As this patient had no medical history of congestive heart failure, liver cirrhosis, and renal disease such as renal failure and nephritic syndrome, so it was excluded out the hypervolemic hyponatremia. There were no clinical conditions of severe burns or gastrointestinal losses from vomiting and diarrhea, hypovolemic hyponatremia was also excluded. Further classification suggested euvolemic hyponatremia. 3) The treatment was hypertonic saline. Corrections have been made in line 93-96 and line 111-114 of the manuscript accordingly.

2. The clinical description suggests that the patient developed delayed motor symptoms, some days after onset of EPM. The authors might wish to elaborate on this unusual aspect and its possible pathogenesis.

R: Thank you so much for your professional suggestions. We have searched for the relative citations, read through the articles seriously. Clinical heterogeneity due to CPM/EPM affecting the basal ganglia has been reviewed by de Souza A[1], such as dystonia, tremor, myoclonus, gait disorders, dysarthria, cognitive impairment, depression and others. Focal oromandibular dystonia and asymmetric myoclonus that developed in a delayed manner in the patient are rare presentations. The possibility that delayed movement disorders may arise in EPM due to ineffective or faulty reorganization in the basal ganglia has been considered in an earlier report[2]. Sequential observation of symptoms and brain images in the case of CPM and EPM revealed that
delayed movement disorders as a result of changes in the signal of the basal ganglia, were explained by the destruction of regional myelin later[3]. Corrections have been made in line 120-127 of the manuscript.

3. What was the basis of using corticosteroid, diazepam and hyperbaric oxygen therapy in the treatment of extrapontine myelinolysis?

R: Thank you so much for this question. We know that no definitive treatment for osmotic demyelination syndrome (ODS) exists and when it develops unexpectedly, the management is to delay or prevent the progression and to improve the symptoms of the patient. Many articles on the treatment are case reports or small series. Some basis was as follows: 1) Steroids are recommended on the basis of rat experiments in which dexamethasone prevented the development of ODS[4, 5]. 2) Previous cases shared the experiences of treating CPM with hyperbaric chamber treatment which might reduce myelin sheath destruction, accelerate cell regeneration, and decrease edema in the injured regions[6]. 3) Both the dystonia and myoclonus in this patient can be the cause of significant disability, and as the etiology of EPM can not be reversed or treated effectively, then symptomatic treatment may be warranted. The involuntary movement of dystonia and myoclonus is thought to have their circuit abnormality in the basal ganglia. The basal ganglia possess GABAergic pathways, and presumably, diazepam performs its therapeutic action through the pathways. However, we can not thoroughly assess the outcomes of these methods, due to the limited number of cases.

4. The case report does not permit one to draw conclusions such as “hyponatremia is the most frequent electrolyte disturbance observed in hospitalized patients.” Or “Osmotic myelinolysis is most frequently associated with rapid correction of hyponatremia.” A citation needs to be included with each statement.

R: Thank you so much for your rigorous academic attitude and suggestion. A citation has been included with each statement accordingly in line 143 and 145 of the manuscript.

5. The authors might like to elaborate on whether the use of pituitrin or DDAVP is associated with a risk of osmotic demyelination independent of the electrolyte disturbance.

R: Thank you so much for your considerate suggestion. Although the true etiology of CPM/EPM remains unclear, abrupt osmotic shifts have been considered to play a critical role in its pathogenesis. DDAVP and pituitrin may predispose patients to osmotic demyelination by causing hyponatremia and ultimate serum sodium fluctuations rather than by exerting any direct myelinolytic effect. Further studies are needed to clarify whether the use of pituitrin or its analogue is associated with a risk of osmotic demyelination independent of the electrolyte disturbance. Corrections have been made in line 136-141 of the manuscript.

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Responses to reviewer Paolo Ragonese:

Thank you so much for your positive comments on the quality of written English. The other detailed and constructive comments are of great help for us to revise the manuscript better.

1. The authors should detail better the causes that lead to the necessity to use the pituitrin.

R: Thank you so much for your considerate suggestion. The causes that lead to the necessity to use the pituitrin are as follows: 1) the patient contracted repeated hemoptysis for five days before admission with conventional therapy of aminomethylbenzoic acid and etamsylate without efficiency. 2) The condition worsened with a massive hemoptysis on admission, which is a life threatening emergency, so pituitrin with the property of strong vasoconstriction was prescribed urgently. 3) Further assessment of the origin of hemoptysis by the CT and CTA of the chest showed the right bronchial artery a little dilated. A multidisciplinary consultation suggested expectant treatment with pituitrin instead of bronchial artery embolization. The former two reasons had been described in the "case presentation" part before, and the latter was added accordingly in line 88-90 of the manuscript.

2. Moreover they did not describe if the patient had a comorbid condition that could increase the risk for
myelinolysis.

R: Thank you so much for your suggestion. This patient had no comorbid conditions such as alcoholism, malnutrition, liver or renal insufficiency that could increase the risk of myelinolysis. We have added the description in line 82-83 of the manuscript accordingly.

3. Literature review needs to be updated.

R: Thank you so much for your serious suggestion. The literature review has been updated accordingly.

4. Reference list and formatting should be corrected.

R: Thank you so much for your suggestion. The reference list and formatting have been corrected accordingly.

References:

1. de Souza A: Movement disorders and the osmotic demyelination syndrome. *Parkinsonism Relat Disord* 2013, **19**(8):709-716.


