Author’s response to reviews

Title: Symptomatic Hyponatremia after Lateral Medullary Infarction

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Author’s response to reviews: see over
Dear Editor

My colleagues and I thank you and the reviewers for your interest in our case report and favorable comments on our manuscript. I am respectfully submitting our revised manuscript, entitled “Symptomatic hyponatremia after lateral medullary infarction.” As you kindly provided us with the chance to revise our manuscript, we have carefully reviewed the insightful comments from the reviewers and corrected the manuscript according to the suggestions. We hope that we have answered the reviewers’ questions adequately. We showed these changes by highlighting in yellow in the manuscript. We hope that you and the reviewers find our manuscript satisfactorily revised and worth publishing in BMC Neurology.

Sincerely,

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Comments for the authors:

Reviewer 1:
1. Treatment of SIADH is fluid restriction not salt restriction. It was mentioned twice in article as salt restriction.
   Thank you for your accurate comment, and we corrected our manuscript as you pointed out.
   In page 2, 4, 8, 10

2. MRI of brain, second figure does show another hyperintense DWI signal at right lateral cerebellum. This does not seem to be an artifact. There was no comment about it. Also, the author may mention if ADC map was performed to correlate with the second lesion.
   The two MRI findings are taken at the same time, and the lesion at right cerebellum was considered as an artifact because it was neither correlated with clinical manifestation nor dark on ADC map.

Minor Essential Revision:
1. It may be helpful if we know patient had history of alcohol abuse or no, since that may predispose to hyponatremia in the first phase.
   Thank you for your accurate comment. The patient had a history of social alcohol drinking. Whether alcohol drinking history affected the progression of hyponatremia in this patient is uncertain, but the initial serum sodium level was little lower than normal (131mEq/L). We modified our manuscript as follows:
   In page 4, 4th line:
   His previous medical history was unremarkable and he was a social drinker. He received oral aspirin 300mg, atorvastatin 20mg and intravenous hydration with normal saline 1 liter per day.

2. Authors may explain why we do not see hyponatremia in most patients with Walenberg syndrome. There should be other reason(s) in this patient predispose him to CSW. If, in fact, he had more than one stroke (seen based on MRI), is that contributing
Thank you for your accurate comment. There has been a case report of SIADH after Wallenberg syndrome as we mentioned in our manuscript (Nomoto N et al, Eur Neurol 2005). However SIADH followed by CSW or CSW by itself has not been reported. We think that the exact location of infarction might be an important factor in sodium homeogenesis. The initial SIADH due to nucleus tractus solitarius (NTS) involvement and later CSW due to the disruption of sympathetic projection from hypothalamus might be a plausible hypothesis. Since mild hyponatremia is asymptomatic and usually improved by fluid restriction, Wallenberg syndrome patients with mild hyponatremia might have been overlooked by clinicians. Many stroke patients are combined with medical conditions which could be associated with hyponatremia, such as diuretics medication, heart failure and renal disease. It is often hard to determine the exact etiology of hyponatremia. The reason why he had progressed to CSW is not certain, but lateral medullary lesion might have progressed slightly with delayed involvement of sympathetic tract. Mild water retention during the initial period of SIADH and normal saline infusion might have stimulated BNP release, which could have precipitated salt wasting afterwards. It is suspected that he was combined with both SIADH and CSW initially. This seems more plausible when considering he was not responding fluid restriction. We modified our manuscript as follows:

In page 6, 8th line:

The reason why he had progressed from SIADH to CSW is a matter of discussion. Initial hydration and mild water retention during the period of SIADH might have stimulated BNP release, which could have precipitated salt wasting afterwards. It is conceivable to suspect that he was initially combined with both CSW and SIADH because he did not respond to water restriction.

Reviewer 2:
Major Compulsory Revisions
1) It is not entirely clear that the patient had SIADH which progressed to cerebral salt wasting. The distinction between the two entities is still controversial in some circles (Sterns and Silver JASN February 2008 vol. 19 no. 2 194-196).

We agree with your point that distinction between SIADH and CSW is not easy in this case, but there were two clear stages of hyponatremia which could be differentiated by volume status and urine concentration. He was diagnosed initially as SIADH because he was not dehydrated and urine was inappropriately concentrated despite low serum osmolality. Later the diagnosis was changed to CSW because he was not responsive to fluid restriction and volume loss was significant: he lost almost 4 kg within one week. We added following description:

In page 5, 6th line:

This patient was diagnosed with SIADH because he was not dehydrated initially and urine was concentrated inappropriately, but later, the diagnosis was changed to CSW because he was not responsive to water restriction and volume loss was evident.

There are several factors which could affect the patients serum sodium and volume status which were not addressed – when patients are admitted for acute ischemic stroke, IV fluids are generally given – if this was done, what fluids and how much were given? Was there any evidence of intrinsic renal disease? Did the patient have any concomitant cardiac disease – heart failure may also stimulate ADH secretion, and potentially fluctuations in cardiac output may have influenced serum sodium and volume levels.
His previous medical history was unremarkable and there was no evidence of intrinsic renal disease or heart failure after admission. We treated him with aspirin 300mg, atorvastatin 20mg, and intravenous hydration of normal saline one liter per day after admission. We supplemented our manuscript as follows:

In page 4, 4th line:
**His previous medical history was unremarkable and he was a social drinker. He received oral aspirin 300mg, atorvastatin 20mg and intravenous hydration with normal saline 1 liter per day.**

If the authors wish to propose a transition from SIADH to CSW this argument needs to be strengthened and supported in the discussion. Otherwise, perhaps it would be best to simply describe and discuss the fluctuations in sodium and volume status that were seen with the medullary lesion – an observation that is very interesting in and of itself.

Thank you for your thoughtful comment. The reason why this patient experienced a transition from SIADH to CSW is not certain but there are several hypotheses. First, the infarction might have progressed to engulf sympathetic projection which was not initially involved completely. The disruption of sympathetic projections will attenuate renal sodium reuptake, mitigate the activation of renin and aldosterone system, and release natriuretic factors inappropriately. However it seemed less likely because the patient had already been combined with Horner syndrome suggesting sympathetic tract disruption from initial admission. Second, initial hydration with normal saline and mild water retention during the SIADH period might have stimulated BNP release, which could have precipitated salt wasting afterwards. Lastly it is conceivable to suspect that he was combined with both CSW and SIADH initially considering that he had not responded to water restriction. To prove our hypothesis, it is necessary to evaluate the presence of hyponatremia depending on whether the lesion involved NTS and/or descending sympathetic projection in a prospective study. It might have been helpful to examine serial serum level of AVP and BNP to assess signals related to sodium homeostasis. We strengthened our manuscript as following:

In page 6, 8th line:
**The reason why he had progressed from SIADH to CSW is a matter of discussion. Initial hydration and mild water retention during the period of SIADH might have stimulated BNP release, which could have precipitated salt wasting afterwards. It is conceivable to suspect that he was initially combined with both CSW and SIADH because he did not respond to water restriction.**