APM ANNALS OF PALLIATIVE MEDICINE
AN OPEN ACCESS JOURNAL FOR HIGH-QUALITY RESEARCH IN PALLIATIVE MEDICINE
IMPACT FACTOR 2.595

**Peer Review File**
**Article Information: https://dx.doi.org/10.21037/apm-21-2025**

**Reviewer A**

**Comment 1**: The authors report a case of a patient with bipolar affective disorder (BD) on lithium maintenance therapy as mood-stabilizer. She had developed lithium-induced nephrogenic diabetes insipidus (NDI) and suffers of venous thromboembolism (VTE) during an episode with dehydration and hypernatremia. The case is well documented and the treatment of both the underlying condition and the VTE exemplarily. Lithium as a risk factor for VTE is clinically debated, but published evidence is sparse. This case undeniably adds evidence to and raises awareness for a rare combination of comorbidities with high clinical relevance and I strongly support its publication. Though, there are some major concerns and the need for some minor corrections.

The major concern is that the scope of the report needs to be more clearly emphasized. Classically, thrombosis is seen as a result of the Virchow´s triad, alterations in blood flow (ie, stasis), vascular endothelial injury and alterations in the constituents of the blood. Broken down to modern medicine, the identified risk factors for VTE are many. For instance, over half of the cases of VTE could be attributed to "institutionalization (current or recent hospitalization or nursing home residence)" in a population-based, nested, case-control study (Heit JA et al. 2002), a condition fulfilled in the current case. Hence, proof of causality - and exclusion of alternative aetiologies - cannot be established in the presented case.

I suggest to focus on the specific setting of BD, lithium treatment and NDI. Lithium leads to renal concentration deficits in a relatively many patients on long-term therapy, some of them having serious forms of NDI. Despite NDI being a classic side effect of lithium, hypernatraemia even occurs in patients with BD without current or former lithium exposition. Interestingly, NDI appears only in the minority of episodes to be the cause of hypernatraemia even in lithium-treated patients (Ott et al. 2019).

Sodium disturbances are most often related to hydration, and not to alterations of body sodium. Here, the wording needs to be semantically unambiguous. Dehydration

leads to hypernatreamia, but not to renal insufficiency. Hypovolaemia causes prerenal renal failure, but not hypernatreamia. Your patient had probably both:
1) loss of free water due to NDI in combination with the inability to maintain fluid intake during her manic episode
2) hypovolaemia, causing reduced perfusion of the kidneys with consecutive prerenal AKI and reduced GFR. This then lead to reduced Li elimination and high serum levels.
Thiazides in that situation might be contraindicated. Correction of hypovolaemia would preferably be cristalloid intravenous fluid.

When discussing aetiology and the pathomechanism of the VTE, I would like to have classic risk factors addressed: previous VTE in the patient´s history? Obesity? Is there any BMI available? Any investigation of thrombophilia, e.g. Factor V Leiden mutation? Not sure about the prevalence in Korea, but Choe et al. reported a case 2019 (PMID: 31305418) Family history? Did her drowsiness lead to immobilisation during the preceding hospitalisation?

The upregulation of genes in vivo is an interesting aspect and to discuss it here makes this case stand out. But this pathomechanism should be attributable to all episodes of hypernatremia irrespective of genesis, right? And hypernatremia is common, as you correctly state in the introduction. The only study addressing dehydration as cause for VTE I found with a quick search in PubMed is Elias et al., 2016. Please add a line in the discussion, why this possible causation has been overlooked so many years. Well, if it exists....

**Reply 1**: We appreciate the reviewer's important comment. We totally agree with your comments.
First, as you mentioned, there are many risk factors for VTE. However, the patient was alert and was able to do all physical activity before the event. In addition, the patient had no disease history except bipolar disorder, no medication history except bipolar disorder treatment and no family history of thromboembolism and hematological disease. The patient's BMI was 21.4kg/m$^2$. The patient became drowsy the day before transfer. Therefore, we determined that the patient had no other risk factors except for hypernatremia and dehydration. We added some data (Page 5, line 77-78).
Second, as you mentioned, NDI appears only in the minority of episodes to be the cause of hypernatremia. We hypothesized that dehydration and hypernatremia were reached because the patient was admitted to a local psychiatric clinic and was not drinking enough water because the patient's activity was limited.

Third, as you mentioned, the patient had both dehydration and hypovolemia. As described in the paragraph above, dehydration was induced due to NDI during restricted activity. AKI was caused by hypovolemia. Five days before admission to our clinic, AKI was diagnosed, and the patient was given IV Hartmann solution sufficiently for 5 days before transfer. Her creatinine level was 3.1 mg/dl on the day she was transferred and improved to 2.37 mg/dl on the day thiazide was given. We assumed AKI and signs of hypovolemia were improved. So we added thiazide for the treatment of nephrogenic diabetes insipidus.

**Changes in the text**: We added some data (Page 5, line 77-78). We revised the paper to highlight the above points. (Page 5, line 79-81). We also added the study for reference (Elias S et al., *Clin Appl Thromb Hemost*. 2016) and revised the discussion. (Page 8, line 148-149/ Page 9, line 166-168)

Minor revisions:

**Comment 2**: Line 1-2: I recommend to replace "Thrombosis" by either "Venous thromboembolism" or "Deep vein thrombosis with pulmonary embolism" since the former does not account for the severity of the observed pathology. The "with" should rather be an "and".
**Reply 2**: We appreciate the reviewer's important comment. We revised the title by referring to the comments of Reviewer 1 and Reviewer 2.
**Changes in the text**: We have modified our text as advised (Page 1, line 3-5).

**Comment 3**: Line 27-28: Not sure which admission is reported. The 1:st or 2nd? Rephrase?
**Reply 3**: We appreciate the reviewer's important comment. The patient was admitted to a local psychiatric clinic first, and was transferred to our clinic.
**Changes in the text:** (Page 3, line 34-35)

**Comment 4**: Line 31-32: Uosm 231 is not really low. Add "inadequately": inadequately low urine osmolality (osmolality, 231 mOsm/kg). UNa is too low in that situation, same applies here.
**Reply 4**: We appreciate the reviewer's important comment. According to the diagnosis of diabetes insipidus, urine osmolarity < 250 mosmol is defined as a clue of diabetes insipidus. Hence, we also described the patient's urine osmolality as 'low' urine osmolality (reference: Leroy C, et al. Diabetes insipidus. Ann Endocrinol (Paris). 2013 Dec;74(5-6):496-507.). In addition, as the definition of euvolemia, the

standard for urine sodium is above 20 mEq/L. Hence, we described the patient's urine sodium as 'normal' urine sodium (reference: N AK, et al. Comparison between Urine Sodium and Clinical Evaluation to Assess Saline Responsiveness in Severe Hyponatremia - A Prospective Study. J Assoc Physicians India. 2019 Apr;67(4):17-20.).

**Comment 5**: Line 40: "resulting" implies causality. Change to "and". Change "PTE accompanied by DVT" to VTE. The normal pathophysiology is DVT first, and PTE as a complication of DVT.
**Reply 5 and changes in the text**: We appreciate the reviewer's important comment. We revised the sentence. (Page 3, line 47-48)

**Comment 6:** Line 59: Hypernatraemia is in most patients the laboratory expression of dehydration, namely the same thing. Simply start the sentence "Signs of dehydration include decreased skin turgor ..."
**Reply 6 and changes in the text**: We appreciate the reviewer's important comment. We revised the sentence. (Page 4, line 63-64)

**Comment 7:** Line 64: "secondary" implies causality. Change to "in the presence of"
**Reply 7 and changes in the text**: We appreciate the reviewer's important comment. We revised the sentence. (Page 4, line 69)

**Comment 8:** Line 65: Be consistent: Li 1,52 is supratherapeutic in the abstract and "intoxication" in the introduction. Decide which terminology to use. Ott et al. 2016 defined intoxication as Li >= 1.5 if you feel you need a reference.
**Reply 8 and changes in the text**: We appreciate the reviewer's important comment. We revised the sentence. (Page 4, line 70)

**Comment 9:** Line 70: The dosage of lithium (300 mg) is irrelevant. Serum levels depend on renal function. If you can provide serum concentrations, it would be of value. You state later 1 -1.2 mmol/l as target concentration. Otherwise the time on lithium is sufficient (>10y)
**Reply 9:** We appreciate the reviewer's important comment. We totally agree with your comment. However, the patient was not regular hospital visitor and never conducted serum lithium concentration before. The dosage of lithium provided was the last dosage she taken at the local psychiatric clinic. Prior to the event, the patient had normal renal function (baseline creatinine: 0.8 mg/dl).
**Change in the text**: We added this information. (Page 5, line 75-81)

**Comment 10:** Line 89: replace "normal" through "therapeutic interval". Normal is actually the absence of lithium in the body.
**Reply 10 and changes in the text**: We appreciate the reviewer's important comment. We revised the sentence. (Page 6, line 99)

**Comment 11**: Line 103: The treatment of the polyuria with a thiazide is an interesting detail. As you clearly show in fig 2 it lacked effect. That is completely in line with my clinical experience. Be aware that a reader might miss that information. Diuretics are contraindicated in the presence of hypovolaemia and AKI!
**Reply 11**: We appreciate the reviewer's important comment. We totally agree with your comment and we should have provided more detailed information of her previous admission before our clinic. Five days before admission to our clinic, acute kidney injury was diagnosed as serum creatinine rose from 0.8 mg/dl to 1.5 mg/dl. So she was given IV Hartmann solution sufficiently for 5 days before transfer. Her creatinine level was 3.1 mg/dl on the day she was transferred and improved to 2.37 mg/dl on the day thiazide was given. We assumed AKI and signs of hypovolemia were improved. So we added thiazide for the treatment of nephrogenic diabetes insipidus.
**Changes in the text:** We revised the manuscript to give detailed information. (Page 5, line 79-81 / Page 7, line 117)

**Comment 12**: Line 112: add "possibly" before "caused"
**Reply 12 and changes in the text**: We appreciate the reviewer's important comment. We revised the sentence (Page 8, line 132).

**Comment 13:** Line 113-114: Both UNa and Uosm have a wide physiologic range. They are though not "normal" if they are not following the physiologic demand. "Normal" is wrong in the context.
**Reply 13**: We appreciate the reviewer's important comment. According to the diagnosis of diabetes insipidus, urine osmolarity < 250 mosmol is defined as a clue of diabetes insipidus. Hence, we also described the patient's urine osmolality as 'low' urine osmolality (reference: Leroy C, et al. Diabetes insipidus. Ann Endocrinol (Paris). 2013 Dec;74(5-6):496-507.). In addition, as the definition of euvolemia, the standard for urine sodium is above 20 mEq/L. Hence, we described the patient's urine sodium as 'normal' urine sodium (reference: N AK, et al. Comparison between Urine Sodium and Clinical Evaluation to Assess Saline Responsiveness in Severe Hyponatremia - A Prospective Study. J Assoc Physicians India. 2019 Apr;67(4):17-20.).

**Comment 14:** Line 114: AKI is not part of NDI (or any diabetes insipidus). Polyuria is.
**Reply 14 and changes in the text**: We appreciate the reviewer's important comment. The patient had polyuria due to NDI. We revised the sentences. (Page 8, line 133-134)

**Comment 15:** Line 117: "adequately" or "adequate amounts of"
**Reply 15 and changes in the text**: We appreciate the reviewer's important comment. We revised the sentence. (Page 8, line 139)

**Comment 16:** Line 125: Natalia is the first name of Dr. Dmitrieva. Idem line 130.
**Reply 16 and changes in the text**: We appreciate the reviewer's important comment. We revised the sentence. (Page 8, line 150/ Page 9, line 156)

**Comment 17:** Line 142 -146: The information cited is no longer accurate. I suggest skipping the discussion concerning treatment of VTE in regard to specific clinical situations as it definitively is out of limits for a case report.
**Reply 17**: We appreciate the reviewer's important comment. We deleted the part recommended.

**Comment 18:** Line 147: "complicated", add "possibly" before "caused".
**Reply 18 and changes in the text**: We appreciate the reviewer's important comment. We revised the sentence. (Page 9, line 173)

**Comment 19:** Line 150: CT venography is hardly consensus, cf. line 142. In my humble opinion, ANY patient presenting with clinical signs of VTE needs a work-up. Wouldn´t it be better to emphasise the need to be aware that patients with NDI need free water - sometimes much so, 10 litres/d are possible - and when they aren´t able to drink, they probably should get it via tube or intravenously? Prevent dehydration!
**Reply 19 and changes in the text**: We appreciate the reviewer's important comment. We totally agree with your comment. We revised the sentence to emphasize the need for prevention of dehydration (Page 10, line 174-175).

Reviewer B

I have read the paper with interest, but I have some comments and questions.

**Comment 1:** The authors' statement: "This is the first reported case of life-threatening pulmonary thromboembolism (PTE) and deep venous thrombosis (DVT) secondary to severe hypernatremia following lithium intoxication…." is incorrect. The authors cite the paper of Kamijo et al. (2003), who showed that dehydration and hypernatremia caused by nephrogenic diabetes insipidus could lead to lithium-induced thrombosis. These results were confirmed by Wasay et al. (2000).

**Reply 1 and changes in the text**: We appreciate the reviewer's important comment. We revised the sentence of abstract and discussion. (Page 3, line 47-48/ Page 10, Line 174)

**Comment 2**: Renal dysfunction caused by concomitant medications or dehydration is reportedly a risk factor for lithium toxicity (including thrombotic complications) without overdoses (Singer I, Rotenberg D 1973; Wilting I et al. 2005; Ott M et al. 2016). As the authors state, the reported case had been hospitalized in a local hospital for the previous two weeks for behavioral therapy. At this point, a question concerning adequate hydration during this time arises. Apart from this one, other questions are: was she physically active or bed-restrained, and did she require additional sedatives or not? She was admitted with the parameters of acute kidney injury and acute coronary syndrome associated with severe hypernatremia, a coincidence that is improbable to develop during one day. Was the pulmonary embolism a potential sequela of the factors mentioned above?

**Reply 2:** We appreciate the reviewer's important comment.

First, the patient was alert and was able to do all physical activity before the event. The patient became drowsy the day before transfer. She did not require sedatives. We hypothesized that dehydration and hypernatremia were reached because the patient was admitted to a local psychiatric clinic and was not drinking enough water because the patient's activity was limited.

Second, acute kidney injury was diagnosed 5 days before admission to our clinic. At that time, the patient's serum sodium level was 135 mEq/L and cardiac marker was normal range. Serum sodium level were elevated to 171 mEq/L the day before transfer, and elevation in cardiac markers was also detected at that time.

**Changes in the text**: We added some date to give detailed information. (Page 5, line 77-83)

**Comment 3**: Interestingly, at serum creatinine 2.77 mg/dl and sodium 171 mEq/L, her hemoglobin level was 11.9 g/dl, which is presumably artificially increased in this condition. After years on lithium, one could suppose chronic tubular and interstitial changes leading to the development of chronic kidney disease. But, any information on kidney size and morphology is lacking in the paper.

**Reply 3:** We appreciate the reviewer's important comment. Prior to the event, the patient had normal renal function (baseline creatinine: 0.8 mg/dl). Also, the kidney size and morphology was normal on an abdominal CT performed on the first day of admission.
**Change in the text:** We added this information. (Page 6, line 109-112)

**Comment 4:** The authors propose that the D-dimer test is an essential component in diagnosing venous thromboembolism. But, this test is considered a nonspecific marker, with high concentrations in many conditions (e.g., malignancy, sepsis, recent surgery, or trauma, pregnancy, and renal failure). Conversely, high D-dimer concentrations are found in nearly all patients with acute DVTs.
**Reply 4 and changes in the text:** We appreciate the reviewer's important comment. We totally agree with your comment. We tried to express the meaning that D-dimer is an exclusion tool of thromboembolism. We revised the sentences. (Page 9, line 169)

**Comment 5:** I propose a change to the title of the paper (after major revision): "Thrombosis with severe hypernatremia in a patient with lithium-induced nephrogenic diabetes insipidus and acute kidney injury (or exacerbation of chronic kidney injury): a case report."
**Reply 5 and changes in the text**: We appreciate the reviewer's important comment. We revised the title by referring to the comments of Reviewer 1 and Reviewer 2. (Page 1, line 3-5)