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CASE REPORT

Prolonged hypernatremia triggered by hyperglycemic hyperosmolar state with coma: A case report

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Abstract

A man with past lithium use for more than 15 years, but off lithium for two years and not carrying the diagnosis of diabetes mellitus or nephrogenic diabetes insipidus (NDI), presented with coma and hyperglycemic hyperosmolar state (HHS). Following correction of HHS, he developed persistent hypernatremia accompanied by large volumes of urine with low osmolality and no response to desmopressin injections. Urine osmolality remained < 300 mOsm/kg after injection of vasopressin. Improvement in serum sodium concentration followed the intake of large volumes of water plus administration of amiloride and hydrochlorothiazide. Severe hyperglycemia may trigger symptomatic lithium-induced NDI years after cessation of lithium therapy. Patients with new-onset diabetes mellitus who had been on prolonged lithium therapy in the past require monitoring of their serum sodium concentration after hyperglycemic episodes regardless of whether they do or do not carry the diagnosis of NDI.

Key words: Hypertonicity; Lithium; Hypernatremia; Hyperglycemia; Nephrogenic diabetes insipidus

Core tip: Hyperglycemic coma with large losses of body water may aggravate lithium-induced nephrogenic diabetes insipidus (NDI) which had been asymptomatic and undiagnosed for years after cessation of lithium therapy. The development of conditions leading to loss of water and consciousness in patients who were on long term lithium therapy should trigger surveillance for NDI even when they were asymptomatic in the past.

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INTRODUCTION

Hypertonicity resulting from excessive losses of body water through the kidneys, the respiratory tract, the skin, the gastrointestinal tract and/or gain in body solute, causes neurological manifestations that may become life threatening[1,2]. Hypernatremia[3] and hyperglycemia[4] are the two common causes of hypertonicity. Severe hyperglycemia developing on the ground of another condition potentially causing hypernatremia may lead to extreme hypertonicity. We present a patient who developed coma from hyperglycemic hyperosmolar state (HHS) followed by prolonged hypernatremia. Nephrogenic diabetes insipidus (NDI) secondary to chronic lithium intake was diagnosed during the period of hypernatremia. NDI had apparently persisted despite discontinuation of lithium two years prior to the HHS, but had not been diagnosed because of absence of hypernatremia and lack of symptoms of hypertonicity.

CASE REPORT

Calculated values, summary statistics

Calculated values: Serum tonicity (effective osmolarity), mOsm/L[5] = 2 × serum sodium concentration ([Na]) + serum glucose concentration ([Glu])/18. Corrected serum sodium concentration[6]: [Na] at hyperglycemia corrected to a [Glu] value of 100 mg/dL by the use of Katz's[7] correction factor, which computes that a 100 mg/dL rise in [Glu] causes a 1.6 mmol/L depression in [Na]:

$[Na]_{Corrected}$, mmol/L = [Na] + 0.016 × ([Glu] - 100)

Calculated serum osmolarity, mOsm/L[5] = 2 × [Na] + [Glu]/18 + blood urea nitrogen ([BUN])/2.8

Summary statistics: Parametric variables are presented as mean ± SD.

Patient report

A 58-year-old man with bipolar disorder was admitted with HHS and coma. He had been treated in the past with lithium carbonate for more than 15 years. During that period, serum lithium level was 0.72 ± 0.27 mmol/L (36 determinations) with two values, 1.3 and 1.4 mmol/L above the therapeutic range (0.5-1.2 mmol/L); in 22 determinations, average [Na] and [Glu] values were within the normal range (Table 1), with one [Na] value, at 146 mmol/L, above the upper normal limit of 145 mmol/L and one [Glu] value was in the hyperglycemic range (171 mg/dL); and in 15 determinations urine specific gravity was 1.008 ± 0.004. The urine specific gravity of all five urinalyses obtained in the last five years of this period was ⩽ 1.005.

Two years prior to the admission he moved to another town and discontinued the intake of lithium. Two months prior to admission with HHS, he resumed his visits to the outpatient clinics of this hospital after a large left lung mass was diagnosed. Positron emission tomography (PET) study showed a left lung mass, 10.9 cm in diameter invading the left main bronchus and the wall of the left pulmonary artery and involvement of several lymph nodes. Lung biopsy revealed squamous cell carcinoma.

He refused treatment for his tumor and opted for palliative management. He did not carry the diagnosis of diabetes mellitus or diabetes insipidus up to that time. During subsequent outpatient visits, progressive hyperglycemia was noted in. Three successive blood samples (Table 1). He refused admission when [Glu] was 809 mg/dL, but was admitted in deep coma three days later. On admission, blood pressure was 147/87 mmHg and heart rate 87 beats per minute. His mucosae were dry. Initial serum chemistries revealed hyperglycemia and profound hypertonicity (Table 1). In addition, BUN was 67 mg/dL, and serum potassium 3.7 mmol/L, total carbon dioxide 16 mmol/L, creatinine (previously in the normal range) 2.49 mg/dL, phosphorus 6.2 mg/dL, magnesium 4.2 mg/dL, lactate 3.4 mmol/L and calculated serum osmolarity 428.6 mOsm/L. The urine had a specific gravity of 1.016 and contained > 500 mg/dL of glucose, but no acetone. Arterial blood pH was 7.01, P_aO_2 102 mmHg (on nasal oxygen supplementation), P_aCO_2 71 mmHg and calculated bicarbonate 13.2 mEq/L. Chest X-ray showed a large mass in the left lung displacing the trachea to the right and several enlarged noncalcified lymph nodes in both lung fields. These findings were unchanged from those in recent earlier chest X-rays.

He received endotracheal intubation with mechanical ventilation, continuous infusion of insulin and large volumes of hypotonic saline containing potassium chloride. Large urine output was noted from the onset of treatment. Progressive decline in [Glu] was documented (Table 1). In a blood sample obtained four hours after onset of treatment, BUN was 66 mg/dL, serum creatinine 2.33 mg/dL, and calculated osmolarity 418.2 mOsm/L, while a simultaneously measured serum osmolality was 424 mOsm/kg. Following these measurements he received larger volumes of water in his infusions and through a gastric tube.

Hyperglycemia, hypokalemia, and hyperphosphatemia were corrected by 48 h after initiation of treatment. At that time, BUN was 48 mg/dL and calculated serum osmolarity 451.5 mOsm/L. Serum creatinine and magnesium declined progressively and reached normal levels by 72 h after the start of treatment. He was extubated on the fourth hospital day. However,

Table 1 Serum chemistries and calculated values related to tonicity

Time	[Glu]	[Na]	Tonicity	[Na]Corrected
	mg/dL	mmol/L	mOsm/L	mmol/L
-15 to -2 yr[1a]	99.6 ± 22.0	141.1 ± 2.7	287.6 ± 5.6	141.0 ± 2.7
-21 d[1]	235	139	291.1	141.6
-14 d[1]	304	141	298.9	144.3
-3 d[1]	809	135	314.9	146.3
Admission	1236	168	404.7	186.2
+2 h[2]	1141	169	401.4	185.7
+4 h[2]	982	170	394.6	184.1
+10 h[2]	771	165	372.8	175.7
+14 h[2]	650	163	362.1	171.8
+18 h[2]	611	160	353.9	168.2
+22 h[2]	548	165	360.4	172.2
+24-48 h[2]	233.5 ± 151.7	164.0 ± 1.9	341.0 ± 9.7	166.0 ± 3.3
+48-72 h[2]	176.6 ± 72.3	168.0 ± 1.9	345.8 ± 7.6	169.2 ± 3.0
+72-96 h[2]	151.8 ± 23.0	165.3 ± 2.6	338.9 ± 4.7	166.1 ± 2.1
+96-120 h[2]	185.0 ± 99.0	176.5 ± 2.1	363.3 ± 1.3	177.9 ± 0.5
+120-144 h[2]	131	172	351.3	172.5
+144-168 h[2]	135	157	321.5	157.6
+168-192 h[2]	186.5 ± 139.3	158.0 ± 9.9	326.4 ± 27.5	159.4 ± 12.2
+9-14 d[2]	175.5 ± 53.7	146.8 ± 1.8	303.5 ± 4.4	147.9 ± 1.8
+14-21 d[2]	241.3 ± 55.6	143.0 ± 3.9	299.4 ± 7.0	145.2 ± 3.7
+3 mo[2]	240	155	323.3	157.2

[1]Time before admission; [2]Time after onset of treatment; [a]Period of lithium intake; [Glu]: Serum glucose concentration; [Na]: Serum sodium concentration; [Na]Corrected: Serum sodium concentration corrected to a serum glucose level of 100 mg/dL; Values reported as mean ± SD represent 2-22 measurements.

production of copious volumes of dilute urine, confusion and severe hypernatremia persisted despite the combined administration of up to 400 mL per hour of 5% dextrose intravenously and free water by nasogastric tube. Over the four days following normalization of glycemia, he received progressively larger injections of desmopressin (from 1 to 4 mcg), but post-injection urine osmolality values ranged between 139 and 180 mOsm/kg, while [Na] ranged between 164 and 171 mmol/L, [Glu] between 84 and 281 mg/dL and [Na]Corrected between 164.7 and 173.7 mmol/L.

On day seven of admission, simultaneous serum and urine measurements revealed the following values: [Na] 161 mmol/L, serum osmolality 330 mOsm/kg, serum vasopressin 4.6 pg/mL, serum lithium undetectable and urine osmolality 279 mOsm/kg. Immediately following these measurements, he received an injection of 5 units of vasopressin. One hour post-injection, urine osmolality was 290 mOsm/kg. Over the next 20 d, his mental status improved slowly, [Glu] ranged between 69 and 304 mg/dL, while [Na] and [Na]Corrected remained elevated (Table 1).

Hypernatremia improved slowly after increase in water intake and administration of amiloride and hydrochlorothiazide. His last two [Na] values were in the normal range. He left the hospital against medical advice after he was declared competent to make treatment decisions by a Psychiatrist. He was advised to continue the medications for hypernatremia and to have a liberal water intake. Two months later he returned with progressive dyspnea. Computed chest tomography revealed increases in the size of lymph nodes and a large clot in the right pulmonary artery. [Na] was elevated (Table 1). He expired in respiratory failure within 48 h of his last admission. Table 1 shows tonicity values throughout his follow-up.

DISCUSSION

This report of a patient developing protracted hypernatremia following treatment of severe HHS illustrates the following clinical points: (1) the level of hypertonicity can become extreme in patients with HHS that remains untreated for several days; (2) Lithium-induced NDI that remained asymptomatic and undiagnosed for years after cessation of lithium therapy can cause severe hypernatremia in patients who encounter difficulties in consuming adequate volumes of water.

Tonicity of the serum is its property to cause osmotic transfers of water into or out of cells suspended in it. [Na] is, in general, an accurate indicator of serum tonicity[8]. Gain in extracellular solutes other than sodium salts, such as glucose, is the main exception to this rule. Hypertonicity in hyperglycemia should be evaluated in two steps: (1) At presentation, the degree of hypertonicity, which results from extracellular accumulation of solute (glucose)[9] and loss of water through osmotic diuresis[10,11], determines the severity of the presenting clinical manifestations is calculated by the tonicity formula[1,5]; (2) The prescription of the tonicity (*i.e.*, sodium plus potassium concentration) of the replacement solutions should be based on [Na]Corrected[12], reflecting the fact that correction of hyperglycemia without any further changes in the external balances of water and monovalent cations leads to rise in [Na], but decrease in serum effective osmolality[12]. Monitoring of the clinical status and serum chemistries is imperative during treatment of severe HHS[12].

Both serum tonicity and [Na]Corrected were at admission extremely high, indicating profound water deficit, in the patient of this report, who despite infusions of large volumes of hypotonic fluids exhibited subsequently protracted hypernatremia and was eventually diagnosed with NDI by formal testing[13]. Persistently low urine specific gravity values during and after lithium therapy identified lithium as the probable cause of NDI.

Lithium use is associated with a variety of renal functional and structural abnormalities[14,15]. NDI is the most prevalent lithium-induced disorder. Lithium enters the principal cells of the collecting ducts through luminal (apical) epithelial sodium channels (ENaC) and inhibits the signaling pathways that involve glycogen synthase 3-beta causing disruption of the aquaporin-2 structure and function and NDI[16,17].

Amiloride is effective in the prevention and treatment of lithium-induced NDI in part because it is an inhibitor of ENaC, while hydrochlorothiazide affects several transport

proteins[18].

Lithium-induced NDI may persist for years after cessation of lithium therapy[19]. Most available reports have found an association between the duration of lithium use and reduced renal concentrating ability supporting a progressive deficit[20]. Movig *et al*[21] reported that 37% of 75 patients receiving lithium developed polyuria (> 3 L/24 h). Polyuria was strongly associated with simultaneous use of serotonergic antidepressants and duration of lithium therapy. Although lithium-induced NDI is often reversible with median duration of therapy (< 6 years), the renal concentrating defect may be permanent after prolonged (> 15 years) therapy with lithium[22]. In large studies with long term follow-up, approximately 15% of patients using lithium demonstrate an irreversible impairment of renal concentration[22]. Several cases of NDI persistence after discontinuation of lithium therapy have been reported[23-29]. Special care is required for patients with this syndrome when they develop medical conditions preventing spontaneous fluid consumption[28].

Another characteristic of lithium-induced NDI is that it may go undiagnosed for years. Patients are able to compensate for this form of NDI, in which the defect in urinary concentration is usually partial, by consuming large fluid volumes. For example the urine volume that is needed for excretion of a solute load of 900 mOsm at a urine osmolality of 300 mOsm/kg is 3 L and can easily be achieved without the development of hypernatremia by patients with normal thirst mechanism.

Lithium-induced NDI can cause severe hypernatremia[30,31] especially after the development of stressful conditions leading to inability of the patients to drink adequate amounts of fluid. We found three reports of four patients on lithium who developed severe hypernatremia secondary to previously undiagnosed lithium-induced NDI in the immediate post- operative period[32-34]. In contrast to these subjects, our patient had stopped lithium intake two years before his admission.

Finally, our patient illustrates the association of manifestations of diabetes mellitus and lithium-induced NDI. Two patients presenting with clinical manifestations of lithium-induced NDI and diabetic ketoacidosis[35] or severe hyperglycemia[36] have been reported. Potential mechanisms of induction of glucose intolerance by lithium were discussed[36]. In addition to the possibility that lithium triggered the development of diabetes mellitus, it is probable that lithium-induced NDI aggravated the water loss secondary to osmotic diuresis in our patient. In osmotic diuresis osmolality values are higher in urine than plasma in all patients except those with diabetes insipidus who exhibit osmolality values lower in urine than in plasma. Thus, water losses from osmotic diuresis are comparatively larger and the hypertonic state that ensues is comparatively more severe in the patients with diabetes insipidus.

Lithium-induced NDI that remained asymptomatic and undiagnosed for years after cessation of lithium therapy may cause severe clinical manifestations of hypertonicity during clinical episodes affecting the patients' access to fluid intake. If these episodes consist of hyperglycemic emergencies, water loss trough combination of hyperglycemic osmotic diuresis and NDI may be massive leading to severe hypertonicity. Patients with severe hyperglycemia who had been on long-term lithium therapy require prolonged attention to their fluid balance after correction of the hyperglycemic episode.

COMMENTS

Case characteristics

Development of hyperglycemic hyperosmolar state (HHS) with profound coma followed by protracted hypernatremia in a patient who had stopped lithium therapy two years in the past.

Clinical diagnosis

Lithium-induced nephrogenic diabetes insipidus (NDI) diagnosed after correction of the HHS by lack of response of the urinary concentration to a formal vasopressin infusion test.

Differential diagnosis

Other causes of hypernatremia including central diabetes insipidus, persistent osmotic diuresis, and inadequate water intake were excluded by appropriate testing.

Laboratory diagnosis

Extreme hyperglycemia and serum effective osmolarity at presentation was followed by protracted hypernatremia which was shown to be the result of NDI by lack of response of urine osmolality to vasopressin infusion.

Imaging diagnosis

Inoperable lung malignant tumor found in chest X-rays, and computed tomography and positron emission tomography scans.

Pathological diagnosis

Squamous cell carcinoma of the lung found on a biopsy of the tumor.

Treatment

Insulin infusion, large volumes of hypotonic fluids given parenterally, by nasogastric tube, and later by mouth, amiloride and hydrochlorothiazide for the HHS and later the NDI, refusal of the patient to receive treatment for his lung tumor.

Related reports

Reports in the literature suggest that lithium-induced NDI may be permanent after cessation of lithium treatment when the duration of lithium therapy exceeded 15 years, while other reports suggest that lithium-induced NDI may cause severe hyponatremia following episodes of severe hyperglycemia.

Experience and lessons

Patients who had been in the past on long-term lithium therapy are at risk of developing severe hypernatremia during episodes that limit their ability to drink water and should have their serum sodium concentration closely monitored during these episodes even if they had not been diagnosed with nephrogenic diabetes insipidus in the past.

Peer-review

This reviewer thinks that it is worth sharing this case with "prolonged hypernatremia triggered by hyperglycemic hyperosmolar state after discontinuation of lithium therapy" by physicians.

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