CASE REPORT

Severe lithium-induced nephrogenic diabetes insipidus: The diuresis paradox

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We report a case of profound nephrogenic diabetes insipidus (NDI) in which renal resistance to antidiuretic hormone results in dilute polyuria despite normal circulating concentrations. A 28-year-old man with bipolar mood disorder presented to his local clinic with symptoms suggestive of lithium toxicity. Plasma lithium concentrations and thyroid-stimulating hormone (TSH) were taken, but results were not acted upon. One week later, he presented obtunded, severely dehydrated and in renal failure. His plasma lithium concentration was 4.3 mmol/L (toxic threshold >1.5 mmol/L) and TSH >100 mIU/L. After admission to the intensive care unit, including haemodialysis and 12 days of ventilation, he developed profound polyuria, with a peak output of 15 L/day. Amiloride with hydrochlorothiazide adequately reduced the polyuria. Management of lithium-induced NDI remains complex, and includes diuretics, which paradoxically reduce polyuria in this setting. Failure to follow up critical results led to profound morbidity, and is a crucial learning point in this case.

Keywords: nephrogenic diabetes insipidus, lithium toxicity, bipolar mood disorder, renal failure, andtidiuretic hormone resistance, polyuria, amiloride, hydrochlorothiazide, chronic kidney disease, primary hypothyroidism, health system challenges, patient safety, clinical pharmacology, endocrinology

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Diabetes insipidus is a rare and treatable disease, characterised by excretion of large volumes of hypotonic urine.[1] Two potential causes include antidiuretic hormone (ADH) deficiency and renal resistance to ADH. ADH mediates blood pressure regulation, sodium (Na+) homeostasis and renal function.[2] Low blood volume in the left atrium, carotid artery and aortic arch detected by baroreceptors and raised serum osmolality detected by osmoreceptors stimulate ADH release from the pituitary.[3]

Central diabetes insipidus is caused by either inadequate production or release of ADH.[2,4] Nephrogenic diabetes insipidus (NDI) is characterised by the inability to concentrate urine, despite normal ADH production and secretion. Resistance to ADH may occur in the collecting tubules of the nephron, or there may be a defect in the counter-mechanism, resulting from medullary injury or decreased Na+ and chloride (Cl–) reabsorption in the thick ascending limb of Henle.[4] Lithium is the most common cause of NDI, and may cause acute toxicity and/or chronic renal accumulation, both of which manifested in severe forms in this case.[1]

Aside from NDI, toxic effects of lithium involve multiple systems. Nausea, vomiting, diarrhoea and abdominal pain are common gastrointestinal side-effects; endocrine effects include primary hypothyroidism, thyrotoxicosis and weight gain; and dermatologically, acne is not uncommon with chronic use.[5] The neurological effects, however, are the most prolific and serious, ranging from fine tremor and daytime somnolence to mental confusion, gross tremor, dysarthria, hyperreflexia, seizures, cranial nerve involvement and focal neurology. These may be associated with chronic use or acute toxicity. Other toxicities include cardiac arrhythmias, hypotension and albuminuria.[5] Increased duration of lithium use is associated with NDI and chronic kidney disease, with the latter occurring less frequently.[5-7]

Case presentation

We obtained patient informed consent, and conducted a retrospective folder review of a 28-year-old man with an 8-year history of bipolar mood disorder, previously stable on his chronic medication of olanzapine, sodium valproate, orphenadrine and lithium. He could independently perform all of his activities of daily living, but was unable to maintain employment, and was fully supported by his parents, with whom he lived. He had no other comorbidities, was HIV negative and using no other chronic medication. His severe mental illness was managed by a primary healthcare urban community day clinic situated in the Western Cape Province. Plasma lithium concentrations and serum creatinine, which should be monitored 6-monthly, and thyroid-stimulating hormone (TSH), which should be monitored annually, were erratically and infrequently performed (Table 1). Plasma calcium concentrations, which should be performed annually, were never checked. Several months prior to this presentation, his plasma lithium concentration was elevated at 2.7 mmol/L (toxicity threshold >1.5 mmol/L), and no changes were made to his lithium dose thereafter. In breach of recommended monitoring protocols, his renal function was not assessed at this time, although it was normal several years earlier (creatinine 79 µmol/L: normal range 53 - 106 µmol/L) (Table 1).

One week prior to presentation, his mother complained to the clinic that he was walking slowly, had reduced speech and decreased facial expression. Appropriately taken blood work revealed that his TSH was >100 mIU/L (normal range 0.5 - 5.0 mIU/L), serum potassium (K+) was 6.4 mmol/L (normal range 3.5 - 5.2 mmol/L), creatinine was 359 µmol/L, and lithium concentrations were markedly elevated at 4.3 mmol/L, consistent with primary hypothyroidism, acute kidney injury, hyperkalaemia and lithium toxicity. Unfortunately, his results

were not acted upon by his clinic. After a further 1 week, he presented acutely to a tertiary emergency unit.

For 3 days preceding admission, the patient was unable to eat or take oral medication, but drank a small volume of water. No overdose, acute infection or other precipitating factors for renal failure or lithium toxicity were identified. On admission to the emergency unit, he was found to be obtunded, dehydrated and with a severe metabolic acidosis with a pH of 7.0, base excess of –14.9 mmol/L and serum bicarbonate of 12.3 mmol/L. He was intubated and ventilated and transferred to the intensive care unit (ICU). Repeat lithium concentrations had decreased marginally to 4.0 mmol/L, but the hyperkalaemia and renal failure had worsened, with a K+ of 8.6 mmol/L and creatinine of 833 µmol/L, for which he required haemodialysis. After 2 days of haemodialysis, his lithium concentration decreased to 0.6 mmol/L, but remained detectable 2 weeks thereafter. His primary hypothyroidism was managed with thyroxine and tertroxin.

Early in his ICU admission, he developed polyuria ranging between 2.6 L and 4.0 L per 24 hours, raising suspicion of NDI, because of the association with lithium use. His urine osmolality was dilute at 181 mOsm/kg (normal range 500 - 850 mOsm/kg), serum osmolality was 307 (normal range 275 - 295 mOsm/kg), serum Na+ was normal at 140 mmol/L, but his urine Na+ was 69 mmol/L (normal range 20 - 30 mmol/L). As this patient's serum Na+ was normal throughout admission, both primary polydipsia (low to normal Na+) and diabetes insipidus (normal to high Na+) were considered. While in the ICU, the patient was initiated on spironolactone for suspected NDI and mineralocorticoid excess, which is not considered standard of care for NDI.

The patient was transferred from the ICU to the general medical ward on day 16 of admission. His urine output continued to increase, to a peak of 14 L on days 35 and 39 of admission (Fig. 1).

His treating team attempted to match the volume of urine output with intravenous fluids, but he was observed regularly consuming large volumes of water. When the spironolactone was discontinued, his urine output increased. A test dose of desmopressin revealed ADH resistance and excluded central diabetes insipidus, as there was neither a reduction in polyuria nor an increase in urine osmolality. Hydrochlorothiazide was initiated thereafter, resulting in a significant decline in urine output. Since the patient's water intake may have resulted in counter-current washout, it was recommended that his fluid intake be limited to 8 L daily, with a planned reduction by 500 mL each subsequent day. We were unable to observe a response to water limitation, as the patient covertly accessed excess water. Finally, a combination of amiloride and hydrochlorothiazide was administered, resulting in a marked reduction in polyuria and enabling his discharge from hospital (Fig. 1). His discharge creatinine was 411 µmol/L, and has remained elevated to this degree. His bipolar mood disorder has been managed as an outpatient with sodium valproate and clozapine, without lithium.

Discussion

We believe that this is the first case report of severe lithium-induced nephrogenic diabetes in Africa.

Pros and cons of lithium use

Lithium has been used to treat bipolar mood disorder for decades, and despite difficulties in dosing that arise from its narrow therapeutic window and high inter-individual variability, it continues to be used for its effectiveness, especially its ability to ameliorate suicidality. After haemodialysis, our patient had detectable lithium concentrations, explained by its strong tissue binding. In patients with normal renal function, two-thirds of a lithium dose are excreted within 6 - 12 hours, and the remainder much more slowly over 10 - 14 days. Importantly, lithium plasma concentrations may not always correlate with intracellular concentrations, the latter of which determine its effects. This explains why patients with significantly elevated serum lithium concentrations might be asymptomatic.[5] Loading with Na+ enhances lithium excretion and, conversely, Na+ depletion may result in lithium retention. Thiazides may therefore cause lithium retention, which may be counteracted by amiloride.[5] Daily fluctuation of plasma concentrations of lithium at steady state may underestimate the peak concentration by two- to three-fold, explaining how even with a trough within range (0.6 - 1.0 mEq/L), toxic symptoms at peak concentration may be encountered.

Our patient developed primary hypothyroidism, NDI and renal failure from lithium. It is difficult to determine whether renal impairment or lithium toxicity was the inciting event.[8] We found no other causes for his renal failure, and in the absence of obvious risk factors, we suggest that his renal failure was secondary to lithium use. Moreover, although he had prolonged use of lithium, it did not exceed 20 years, further corroborating that his renal failure was likely due to toxic plasma lithium concentrations. Progression of renal failure may have further raised his plasma lithium concentrations, which in turn may have worsened his renal failure and resulted in severe NDI.

Causes of polyuria

Diabetes insipidus and primary polydipsia are the most common causes of polyuria with dilute urine (osmolality <300 mOsm/kg).[9] Primary polydipsia is often encountered in patients with mental illness, and may be psychogenic or secondary to psychotropic medication, which induce dry mouth and excessive thirst.[10] A trial of desmopressin failed to increase urine osmolality by >50% in our patient, excluding central diabetes insipidus.[11] A water deprivation test would have been helpful to exclude primary polydipsia in our patient, but this was not possible, as the patient accessed drinking water despite our instructions to the contrary.

Primary polydipsia results in copious dilute urine 'washing out' solute required to maintain the counter-current mechanism. During a water deprivation test, there is a reduction in the amount of dilute

Table 1. Patient blood results preceding presentation

	Clinic routine visit					Clinic presentation	Hospital presentation
Test	2015	2017	2018	2019	2022	21 June 2023	27 June 2023
Lithium (mmol/L) Normal range 0.4 - 1.2; toxicity >1.5	0.5	0.4	0.5	1.0	2.7	4.3	4.0
K+ (mmol/L) Normal range 3.5 - 5.2						6.4	8.6
Creatinine (mmol/L) Normal range 53 - 106	79.0					359.0	833.0

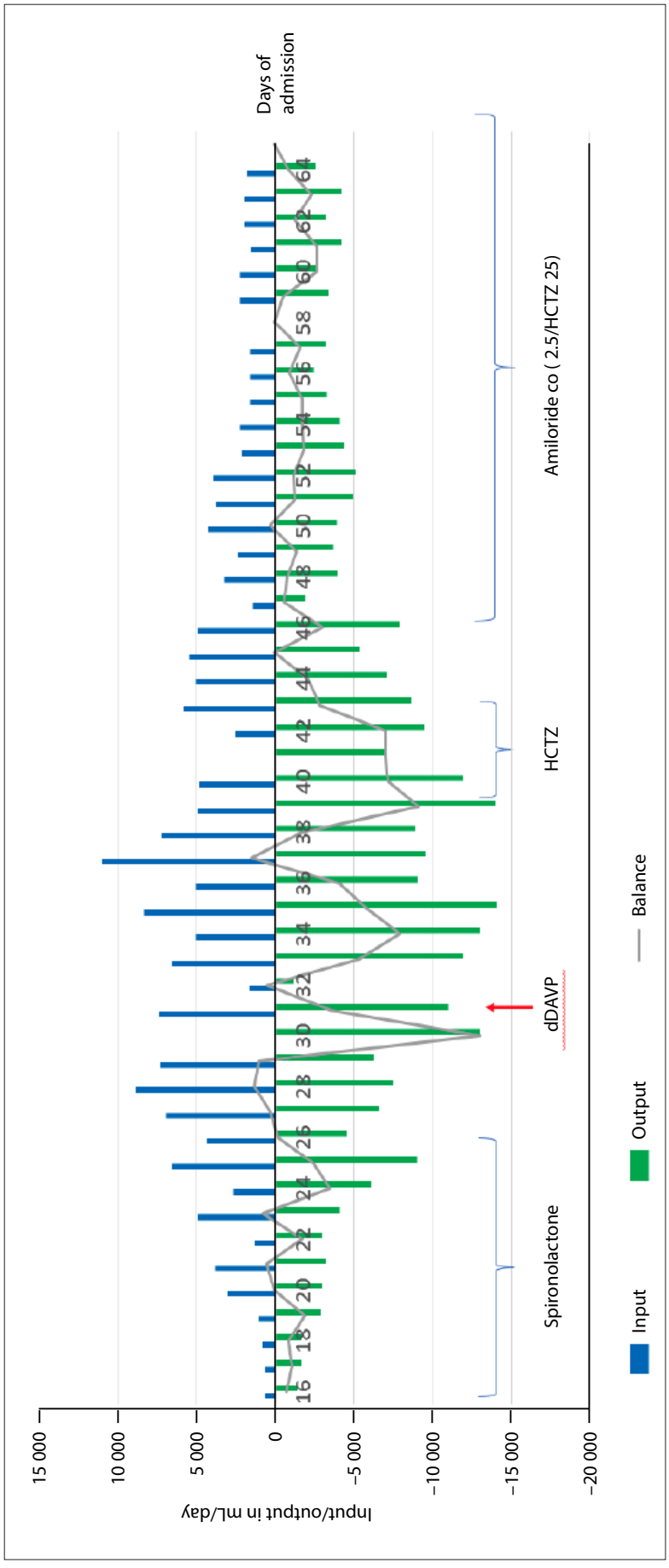

Fig. 1. Fluid intake and urine output during admission to general medical ward (Day 15 - 64) and timing of drug therapy. (dDAVP = desmopressin; HCTZ = hydrochlorothiazide.)

urine reaching the loop of Henle, permitting the gradient to re-establish. Achieving a urine osmolality >800 mOsm/kg is thus indicative of primary polydipsia, provided reduced intake of oral fluids can occur in advance of a water deprivation test.[11] We remained suspicious that primary polydipsia may have contributed to his polyuria, although the pre-eminent cause of the polyuria was deemed to be lithium-induced NDI.

Mechanisms leading to lithium-induced NDI

Lithium enters the principal and proximal tubule cells predominantly via the epithelial sodium channel (ENaC), and can replace Na+ in most transport systems (Fig. 2).[13] The Na+/K+ adenosine triphosphate-ase (ATPase) pump may transport lithium into the plasma, but it easily accumulates within the principal cell. Three mechanisms leading to lithium-induced NDI have been described.[14] Lithium reduces gene expression of aquaporin 2 (AQP2) on the apical membrane, decreasing water reabsorption.[13] Secondly, it inhibits glycogen synthase kinase-3, which increases prostaglandin E2 (PGE2) production. PGE2 inhibits the vasopressin (V2) receptor, leading to ADH resistance.[15] Finally, lithium may cause collecting duct remodelling, with a decreased ratio of principal to intercalated cells, impairing urine concentration.[6] This final mechanism may lead to interstitial nephritis and end-stage kidney disease seen in a small subset of patients.[6]

Management of lithium-induced NDI

Diuretics used to treat NDI are counterintuitive, but effective therapy. We used amiloride and hydrochlorothiazide to treat our patient after an initial trial of spironolactone. Thiazides and amiloride are the mainstay of treatment, and act on the distal convoluted tubule and the principal cells, respectively.[16] Initially, this increases polyuria, inducing a state of mild dehydration, which activates the renin-angiotensin-aldosterone system and stimulates Na+ and proximal water reabsorption.[17-19] Less urine reaches the distal tubule and collecting duct, and a reduced volume is thus excreted. Thiazide diuretics increase AQP2 number and partially inhibit carbonic anhydrase, resulting in an increase in pH through bicarbonate loss.[16] This leads to activation of K+/calcium channels causing vasorelaxation and increased blood flow to the macula densa.[20] Tubulo-glomerular feedback results, reducing the glomerular filtration rate.[20] Amiloride has a special use in lithium-induced NDI, as it blocks the ENaC, preventing lithium from entering the principal cell. Lithium has a higher affinity for the ENaC than Na+ and is preferentially resorbed.[5] In patients with mild NDI who wish to continue treatment

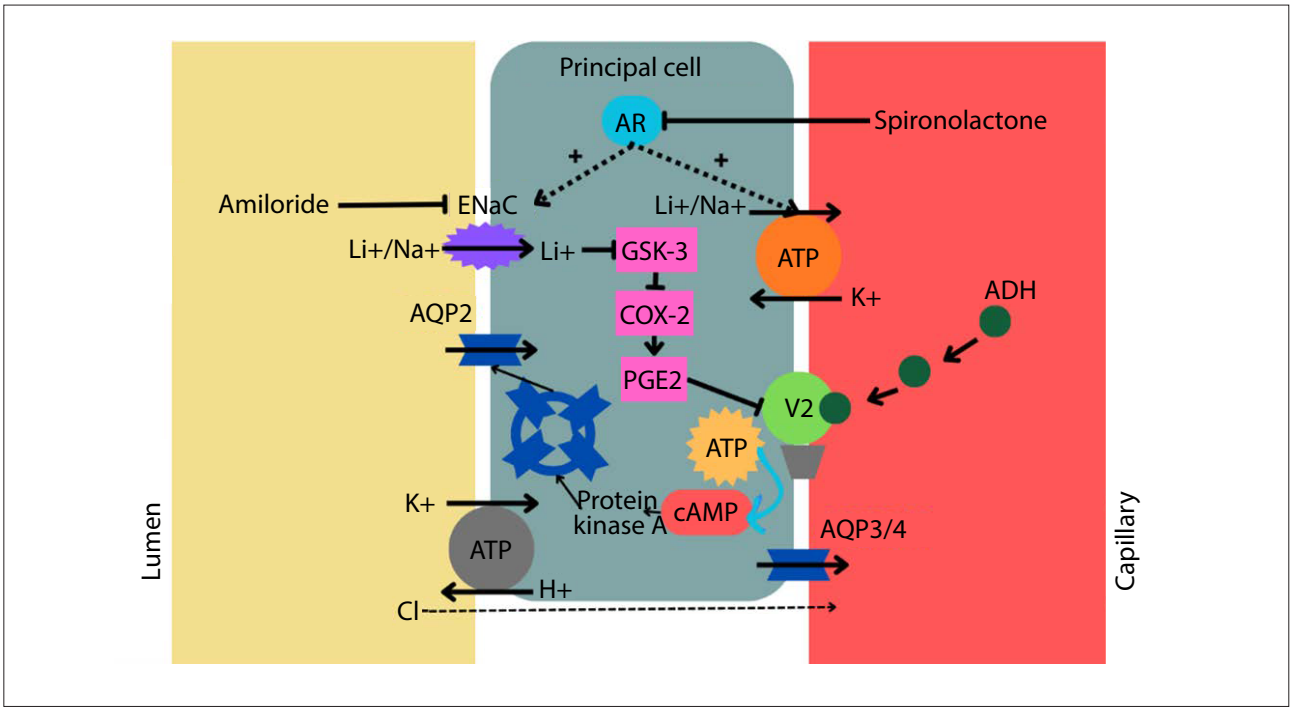

Fig. 2. Pathophysiology of lithium-induced nephrogenic diabetes insipidus in the principal call of the collecting duct. (AR = aldosterone receptor; ENaC = epithelial sodium channel; Li+ = lithium; Na+ = sodium; GSK-3 = glycogen synthase kinase 3; ATP = adenosine triphosphate; ADH = anti-diuretic hormone; COX-2 = cyclo-oxygenase 2; PGE2 = prostaglandin E2; AQP = aquaporin; V2 = vasopressin 2 receptor; K+ = potassium; cAMP = cyclic adenosine monophosphate; H+ = hydrogen ion; Cl = chloride.)

with lithium, amiloride may be useful as adjunctive therapy. In our patient, we aimed to prevent reuptake of lithium into the principal cells through use of amiloride, as there is prolonged mobilisation of lithium from peripheral tissue to the plasma.[13,19,21] Acetazolamide is also a treatment option, but was not utilised in this case as it is not as well tolerated as amiloride/hydrochlorothiazide, and evidence for its use is not as robust.[20,22] Non-steroidal anti-inflammatory drugs may decrease renal prostaglandins, enhancing the action of ADH on the V2 receptor, but are not recommended for their unintended effect of raising plasma lithium concentrations, and may exacerbate renal failure.[15,23]

Health system factors

Monitoring protocols were not followed by the clinic, and although plasma samples were erratically taken, they were neither checked nor addressed on two separate occasions. This failure may be a consequence of an underfunded, understaffed healthcare system that faces multiple challenges.[24] Healthcare workers frequently experience burnout, and there may be increased errors in patient care. Inadequate training of mental healthcare providers may also have contributed to this series of events, and we believe that proactive patient education and family involvement may have permitted early detection of toxicity symptoms. With appropriate follow-up and action, many of these severe adverse consequences of lithium toxicity may have been prevented or ameliorated in our case. The financial implication of this error also burdens our healthcare system. In addition, our patient has newly diagnosed, established chronic kidney disease with a serum creatinine >400 µmol/L, which may have been preventable had monitoring procedures been followed correctly. Our case serves to remind clinicians of the implications of failing to follow up all results, which may have medicolegal implications, lead to serious morbidity and have potentially fatal outcomes.

Teaching points

- Lithium is first-line treatment for bipolar mood disorder in South Africa, but its use is challenging due to its narrow therapeutic window, high potential for toxicity and multiple drug-drug interactions.
- Despite the potential for severe side-effects, it is life-saving.
- We present a challenging case of lithium-induced NDI requiring complex therapy, including administering diuretics that effected a paradoxical reduction in diuresis.
- Mental healthcare users are a vulnerable population, and adequate resourcing of clinics and training of clinic staff are essential to provide good care, monitoring and patient education.
- We encourage conscientious follow-up of critical results, failure of which can result in fatalities, chronic ill-health and economic consequences, which our health system can barely afford.

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Conflicts of interest. None.

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