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Hypercalcemia and diabetes insipidus in a patient previously treated with lithium

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SUMMARY

Background A 65-year-old woman presented with decreased oral intake, a reduced level of consciousness, hypercalcemia and hypernatremia. She had previously received lithium for 20 years for a schizoaffective disorder, but this treatment had been discontinued 3 years before presentation.

Investigations Physical examination, laboratory studies including measurement of serum calcium and parathyroid hormone levels, measurement of urine and serum osmolalities before and after desmopressin administration, blood and urine cultures, and a CT scan of the abdomen.

Diagnosis Urosepsis, dehydration, kidney stone disease, hyperparathyroidism, and nephrogenic diabetes insipidus.

Management Hydration, antibiotics, intravenous pamidronate for rapid control of hypercalcemia, parathyroidectomy, surgical removal of the large kidney stones, a low-protein and low-sodium diet, and initiation of treatment with a thiazide diuretic.

KEYWORDS calcium-sensing receptor, hypercalcemia, lithium, nephrogenic diabetes insipidus, thiazide

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THE CASE

A 65-year-old woman presented to hospital with decreased oral intake and reduced level of consciousness of several days' duration. Her past medical history included a schizoaffective disorder that had been treated with lithium 400 mg/day for 20 years (discontinued 3 years before presentation), hypothyroidism for 8 years, and sagittal vein thrombosis and aphasia for 4 years. She had no history of lithium intoxication.

The patient had previously had polyuria, polydipsia and a daily fluid intake of 5 l. For several years she had required a change of diaper every 4 h, but this need had decreased with the onset of her current illness. On presentation, the patient was taking levodopa–carbidopa, levothyroxine, and flupentixol.

Physical examination revealed a somnolent woman with a Glasgow Coma Scale score of 13, a BMI of 31.2 kg/m^2, hypotension (blood pressure 90/50 mmHg), a heart rate of 120 beats per minute, a respiratory rate of 24 breaths per minute, a temperature of 39 °C, and dry mucous membranes; lung examination revealed diffuse rhonchi. The patient had leukocytosis and positive urine and blood cultures for *Escherichia coli*. Laboratory findings are presented in Table 1.

The patient received intravenous antibiotics and aggressive hydration with 3 l half-normal saline (daily, 0.45% NaCl) for 72 h, which resolved the fever, hypotension, leukocytosis and hypernatremia. Her urinary output of 5 l/day persisted despite fluid restriction to 1 l, under careful observation, for 24 h. The patient received pamidronate to treat the hypercalcemia while she was awaiting parathyroidectomy, and her corrected serum calcium level was 2.4 mmol/l (9.6 mg/dl).

Ten days after the patient presented, her urine specific gravity was 1.010, urine osmolality was 180 mmol/kg, urine sodium was 95 mmol/l, serum osmolality was 31 mmol/kg, and serum sodium was 148 mmol/l. Five hours after subcutaneous administration of 5 μg of desmopressin, urine osmolality remained low

Table 1 Laboratory findings on presentation.

Laboratory parameter	Value
White blood cell count	13.5×10^9/l
Serum sodium	148 mmol/l
Serum chloride	114 mmol/l
Serum potassium	3.6 mmol/l
Serum bicarbonate	28 mmol/l
Blood urea nitrogen	9.3 mmol/l (26 mg/dl)
Serum creatinine	53.0 µmol/l (0.6 mg/dl)
Serum calcium	3.4 mmol/l (13.5 mg/dl)[a]
Serum phosphorus	0.81 mmol/l (2.5 mg/dl)[b]
Serum albumin	36 g/l
Intact parathyroid hormone	50 ng/l (50 pg/ml)[c]
25OH-vitamin D	19.2 nmol/l (7.7 ng/ml)[d]
$1,25(OH)_2$-vitamin D	114.4 nmol/l (44 pg/ml)[e]
Urine calcium	450 mg/24 h
Urine creatinine	1.10 g/24 h
Urine specific gravity	1.010

[a]Normal 2.1–2.6 mmol/l (8.5–10.5 mg/dl). [b]Normal 0.94–1.6 mmol/l (2.9–5.0 mg/dl). [c]Normal 8–76 ng/l (8–76 pg/ml). [d]Desirable 50–150 nmol/l (20.0–60.0 ng/ml). [e]Normal 52–120 nmol/l (20–46 pg/ml). Abbreviations: $1,25(OH)_2$-vitamin D, 1,25-dihydroxycholecalciferol; 25OH-vitamin D, 25-hydroxycholecalciferol.

at 230 mmol/kg. A CT scan of the abdomen showed bilateral renal stones that were larger in the left kidney, but revealed no obstruction.

The patient underwent surgical removal of the left kidney stones and right parathyroidectomy 21 days after admission. A dietician recommended a diet that included 50 g protein, 2 g sodium, and 25 mg of hydrochlorothiazide daily. During the 7-month period after parathyroidectomy, the patient continued to have mild hypernatremia (serum sodium 145–148 mmol/l), and a urine output of 3.5–5.0 l despite normocalcemia (documented by several serum calcium measurements in the range 2.3–2.4 mmol/l [9.0–9.5 mg/dl]).

DISCUSSION OF DIAGNOSIS

Differential diagnosis of hypercalcemia and hypernatremia

The patient presented with hypercalcemia and hypovolemic hypernatremia in the setting of urosepsis and renal calculi. Chronic lithium therapy has been associated with both of these metabolic disturbances.

Calcium is critical to hormone secretion, coagulation, and many cellular and neuromuscular functions. Maintenance of calcium level within a narrow physiologic range is achieved through an inverse sigmoidal relationship between serum ionized calcium and parathyroid hormone (PTH) levels (Figure 1). This relationship is mediated through G-protein-coupled calcium-sensing receptors (CaSRs), which are highly expressed in the parathyroid gland and kidneys.[1] In subjects with normal renal and parathyroid function, increases in serum calcium levels to above 2.5–2.6 mmol/l (10.0–10.5 mg/dl) lead to decreases in intact PTH levels to less than 20 ng/l (20 pg/ml; Figure 1). The elevated calcium and PTH levels in the present case confirmed a PTH-mediated process (Figure 2), and as the levels were in the ranges expected in patients with hyperparathyroidism, other causes of hypercalcemia were ruled out (Figure 1, Box 1). Dehydration, altered mental status, and nephrogenic diabetes insipidus (DI) contributed to the hypercalcemia; calcium levels decreased by 0.25 mmol/l (1 mg/dl) with hydration.

The other observed metabolic abnormality, hypovolemic hypernatremia, resulted from excessive water losses and decreased fluid intake. The patient fulfilled criteria for a definite diagnosis of nephrogenic DI: urine volume >3 l/24 h (or >40 ml/kg body weight), urine osmolality <300 mmol/kg (or urine specific gravity <1.010), failure to concentrate the urine despite a serum osmolality >295 mmol/kg, and lack of urinary concentration following desmopressin administration.[2] Lithium is among the most frequently reported causes of nephrogenic DI; other causes include hypercalcemia, amphotericin B, demeclocycline, foscarnet,[2] and congenital forms caused by mutations of the vasopressin V_2 receptor or aquaporin-2. In the patient presented here, fever contributed to insensible water losses. The patient's low fluid intake at presentation was secondary to urosepsis and altered mental status, preventing compensation for the nephrogenic DI.

Complications of lithium therapy

Lithium, the drug of choice for treating bipolar disorders, has a success rate of 70–80%. Complications of chronic lithium therapy include hypothyroidism, hyperthyroidism, hyperparathyroidism (as in the current patient), nephrogenic DI (as in the current patient), and

weight gain.[3] Less-common renal defects include renal tubular acidosis, renal resistance to PTH, aminoaciduria, proteinuria and reduced glomerular filtration rate.[4]

As lithium has a narrow therapeutic index, with therapeutic serum levels in the range 0.6–1.2 mmol/l, close monitoring is needed. Agents such as nonsteroidal anti-inflammatory drugs, thiazides and angiotensin-converting-enzyme inhibitors decrease lithium excretion and increase its toxicity. Toxicity can manifest as lethargy, drowsiness, weakness, nausea, vomiting, diarrhea, ataxia, impaired consciousness, seizures, renal insufficiency, cardiac arrhythmias, and acute renal failure.[5]

Effect of lithium on calcium metabolism

Lithium increases serum total and ionized calcium and intact PTH levels within weeks, but these remain within the normal range in most subjects.[6,7] Lithium also increases serum magnesium level and decreases urinary calcium and magnesium levels—findings reminiscent of familial benign hypocalciuric hypercalcemia (a syndrome caused by inactivating mutations in the CaSR).[6,8] In addition, lithium decreases parathyroid gland sensitivity to calcium, shifting the set-point of the calcium–PTH curve to the right (Figure 3).[9] Lithium is thought to exert an action downstream of the CaSR, although the precise mechanism by which it interferes with CaSR signaling is unknown. Patients on lithium therapy sometimes develop overt hyperparathyroidism. In a study of 142 Swedish patients who had been on lithium for at least 15 years, the point prevalence of hypercalcemia was 3.6%, that of surgically verified hyperparathyroidism was 2.7%, and the observed incidence of hyperparathyroidism was 6.3% over 19 years.[10] The point prevalence for hyperparathyroidism was 7.5 times greater than that expected in the general Swedish population. Altered calcium sensing would be expected to result in four-gland hyperplasia in patients with lithium-induced hyperparathyroidism. A cumulative evaluation of 50 cases of lithium-associated hyperparathyroidism revealed a hyperplasia prevalence of 38%, in contrast to a reported prevalence of 10–15% in sporadic hyperparathyroidism.[11–13] Another study showed that the median duration of lithium therapy was 2 years in patients with parathyroid adenomas ($n=14$) and 12 years in patients with four-gland hyperplasia ($n=12$).[11] Lithium might unmask adenomas in patients with pre-existing parathyroid lesions within a few years of starting therapy, and might induce parathyroid hyperplasia with more-chronic use.[11]

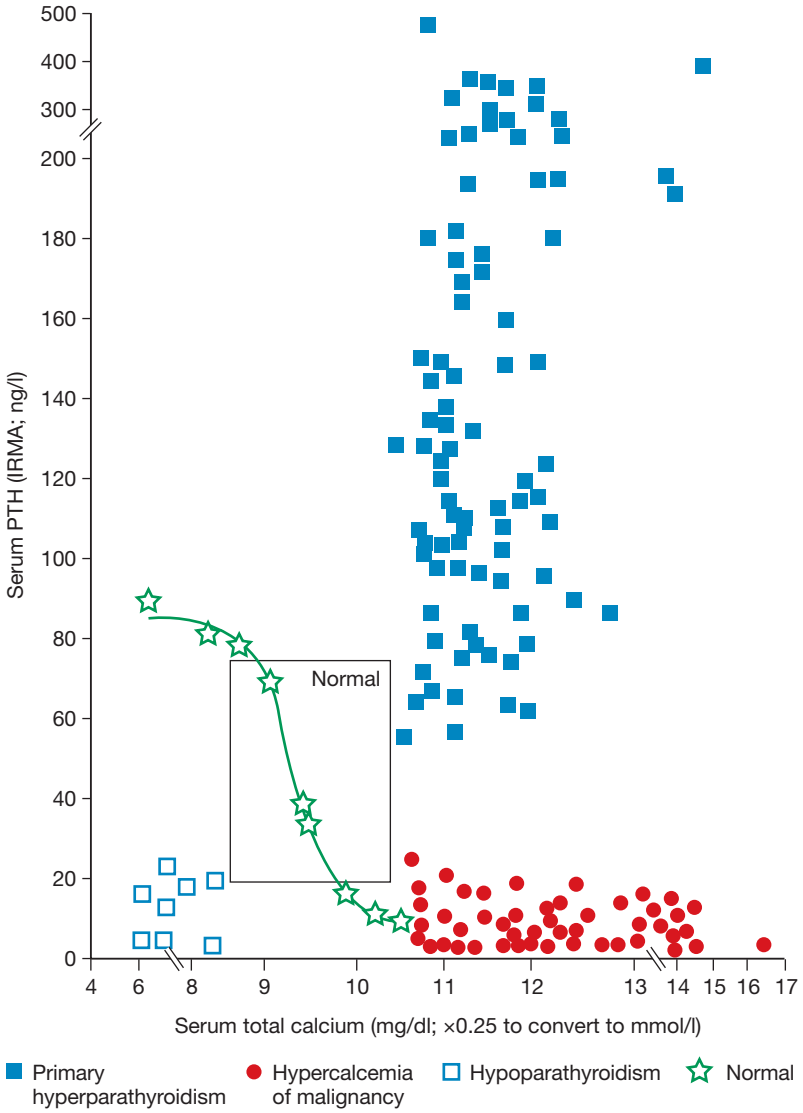

Figure 1 Relationship between serum PTH concentration and serum total calcium concentration in various disease states. Normal ranges are depicted by the box. The sigmoidal curve was derived from a calcium citrate infusion protocol administered to 38 normal subjects. Serum PTH and calcium levels are low in hypoparathyroidism (open squares) and high in primary hyperparathyroidism (filled squares). Serum calcium concentration is high and serum PTH level is low in patients with non-PTH-induced hypercalcemia (filled circles). Abbreviations: IRMA, immunoradiometric assay; PTH, parathyroid hormone. Data for the sigmoidal curve from Haden ST *et al.* (2000) The effects of age and gender on parathyroid hormone dynamics. *Clin Endocrinol* **52:** 329–338. Adapted with permission from: El-Hajj Fuleihan G. Parathyroid hormone secretion and action. In: UpToDate, Rose, BD (Ed), UpToDate, Waltham, MA 2006. Copyright 2006 UpToDate, Inc. For more information visit www.uptodate.com.

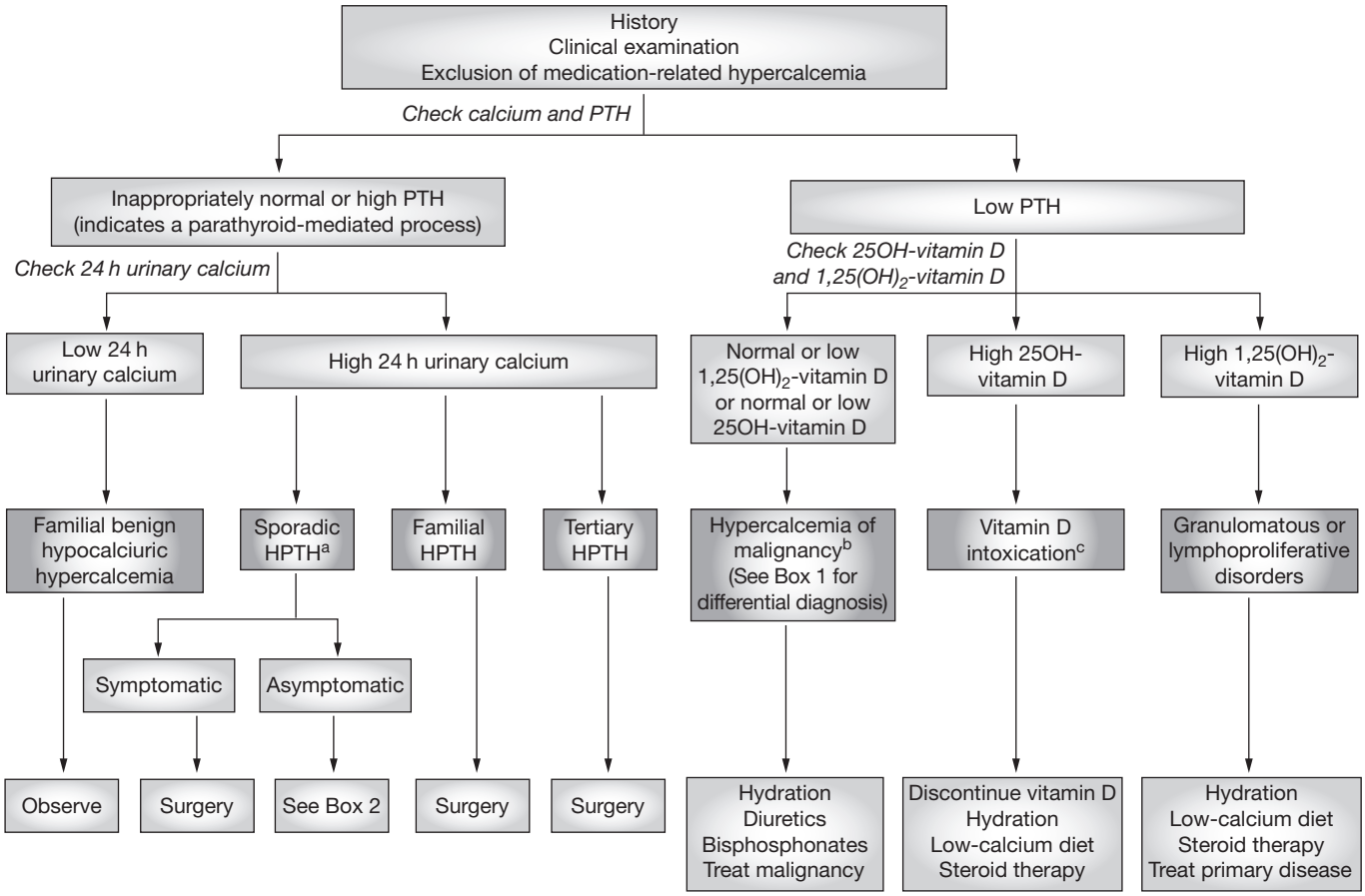

Figure 2 Evaluation and management of hypercalcemia. Major disease categories are depicted in the flow diagram. See Box 1 for rare causes of hypercalcemia. [a]The most common cause of hypercalcemia in the outpatient setting. [b]The most common cause of hypercalcemia in hospitalized patients. [c]$1,25(OH)_2$-vitamin D level might be elevated in cases of vitamin D intoxication. Abbreviations: $1,25(OH)_2$-vitamin D, 1,25-dihydroxycholecalciferol; 25OH-vitamin D, 25-hydroxycholecalciferol; HPTH, hyperparathyroidism; PTH, parathyroid hormone.

Lithium-induced nephrogenic diabetes insipidus

Most cases of nephrogenic DI result from metabolic disorders (e.g. hypokalemia, hypercalcemia), drugs (e.g. lithium, demeclocycline), chronic renal disease or postobstructive diuresis.[2] A study evaluating over 1,000 patients on chronic lithium therapy reported defective concentrating ability in 54% and polyuria in 19% of patients; glomerular filtration rate was usually well preserved.[14]

In the collecting duct, lithium enters renal tubular cells through the amiloride-sensitive epithelial sodium channel in the luminal membrane and accumulates intracellularly.[15] Normally, antidiuretic hormone (ADH; also known as arginine vasopressin) binds to vasopressin V_2 receptors on the basolateral membranes of the principal cells of the cortical and medullary collecting tubules, stimulating cyclic AMP (cAMP) accumulation and insertion of aquaporins (water channels) into the apical membrane, which leads to enhanced water reabsorption.[16]

Lithium interferes with the above cascade by decreasing the production and accumulation of cAMP,[17] downregulating expression of aquaporin-2 channels,[18] and decreasing the density of ADH receptors.[19]

Nephrogenic DI in the context of lithium therapy often results from one or more of the renal effects outlined above. Tubular atrophy and focal interstitial sclerosis have also been described in lithium users and might be the pathologic basis for irreversible DI.[20] DI can also occur secondary to lithium-induced metabolic disturbances such as hypercalcemia (as in the current patient), from polydipsia due to

lithium-stimulated thirst, and from psychogenic polydipsia. Duration of treatment greater than 2 years has been associated with irreversible nephrogenic DI.[2]

The diagnosis of DI in this patient was based on the criteria outlined above. In uncertain cases, and only under close monitoring, a water deprivation test might be helpful to differentiate DI from other major causes of polyuria. Water deprivation is unnecessary, however, and can be dangerous in patients with a high clinical suspicion of DI. A desmopressin test (5–10 μg administered nasally or subcutaneously), with serial monitoring of serum and urine osmolalities, can differentiate central from nephrogenic DI.

Hypercalcemia and nephrogenic diabetes insipidus

Chronic hypercalcemia can cause nephrogenic DI through multiple mechanisms, including acute interference with vasopressin-stimulated water flow, chronic downregulation of aquaporin-2 channel expression in the cortical collecting duct,[21] and direct or indirect (e.g. via prostaglandins) inhibition of sodium chloride reabsorption in the medullary thick ascending limb.[22] Some or all of these actions might be mediated by the CaSR (Figure 4).[1]

DISCUSSION OF MANAGEMENT

Monitoring patients on lithium

Lithium levels should be monitored every 3 months in asymptomatic individuals on lithium. Patients should be monitored for polyuria, polydipsia, and symptoms of thyroid dysfunction; levels of serum creatinine, electrolytes, calcium and thyroid-stimulating hormone should be measured at baseline and yearly thereafter.

Management of lithium-induced nephrogenic diabetes insipidus

If a patient has been on lithium for less than 2 years, it might be possible to replace lithium with other mood regulators. Urinary concentrating defects might be completely reversible if patients have received lithium for less than 1 or 2 years, but they are only partially reversible or are irreversible after chronic lithium use.[2] A precise 'turning point' between reversible and irreversible defects, however, has not been defined.[2] The patient presented here had discontinued lithium after 20 years of use, with no reversal of the concentrating defect.

Box 1 Differential diagnosis of hypercalcemia.

PTH-mediated hypercalcemia
Sporadic primary hyperparathyroidism[a]
Familial hyperparathyroidism
- Isolated familial hyperparathyroidism (including hyperparathyroidism–jaw tumor syndrome)
- Multiple endocrine neoplasia type I: pituitary adenoma, hyperparathyroidism, pancreatic tumor
- Multiple endocrine neoplasia type IIa: hyperparathyroidism, medullary carcinoma of the thyroid, pheochromocytoma
- Familial hypocalciuric hypercalcemia (usually caused by an inactivating mutation in CaSR)

Tertiary hyperparathyroidism

Vitamin D-mediated (nonmalignant) hypercalcemia
Vitamin D intoxication
Calcitriol-producing granulomas (infectious and noninfectious) such as sarcoidosis, silicosis, paraffin-induced granulomas, berylliosis, Wegener's granulomatosis, tuberculosis, candidiasis, histoplasmosis, cat scratch disease and leprosy

Malignancy-induced hypercalcemia[b]
PTH-related-peptide-mediated: squamous cell carcinomas
Calcitriol-mediated: malignant lymphoproliferative disorders
Local osteolytic metastasis: caused by cytokines such as tumor necrosis factor and interleukin 1

Medication-related hypercalcemia
Lithium
Thiazides
Parathyroid hormone
Vitamin A intoxication
Estrogens and antiestrogens in breast cancer
Aminophylline intoxication

Miscellaneous
Milk–alkali syndrome
Pheochromocytoma
Hyperthyroidism
Addison's disease
Immobilization (e.g. in Paget's disease of bone or in the case of multiple fractures in a growing skeleton)
Volume contraction

[a]Most common cause of hypercalcemia in the outpatient setting. [b]Most common cause of hypercalcemia in the hospital setting. Abbreviations: CaSR, calcium-sensing receptor; PTH, parathyroid hormone.

In lithium users, the potassium-sparing diuretic amiloride can be used to prevent intracellular lithium accumulation by blocking sodium channels in the cortical collecting duct. As the patient presented here had been off lithium for 3 years, amiloride was not an option.

Thiazide diuretics can be used to induce mild volume depletion. Volume depletion increases proximal solute reabsorption, thereby decreasing

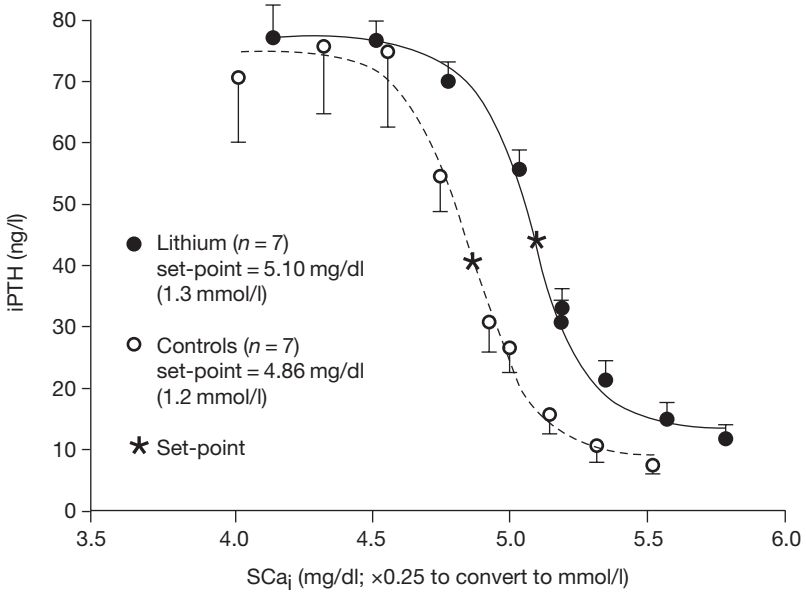

Figure 3 iPTH dynamics in lithium-treated and control groups. The sigmoidal curves were generated from the 30-minute time points during citrate and calcium infusions, when SCa_i levels were stable. Abbreviations: iPTH, intact parathyroid hormone; SCa_i, serum ionized calcium. Permission obtained from The Endocrine Society © Haden ST *et al.* (1997) Alterations in parathyroid dynamics in lithium-treated subjects. *J Clin Endocrinol Metab* **82:** 2844–2848. Copyright 1997, The Endocrine Society.

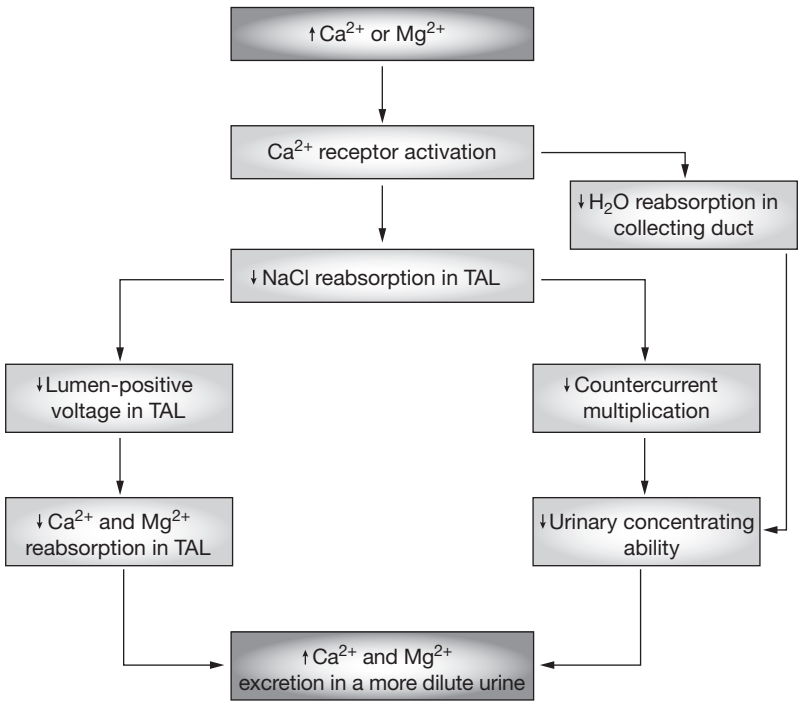

Figure 4 Hypothetical mechanisms that might coordinate systemic calcium and water homeostasis in humans. The diagram illustrates renal mechanisms through which the calcium-sensing receptor might inhibit maximal urinary concentrating capacity. Abbreviation: TAL, thick ascending limb. Permission obtained from The American Physiological Society © Brown EM and MacLeod RJ (2001) Extracellular calcium sensing and extracellular calcium signaling. *Physiol Rev* **81:** 239–297

delivery of water to the collecting ducts and reducing urine output. Thiazide diuretics also upregulate aquaporin-2 channel expression;[23] however, as these drugs lower urinary calcium excretion and might exacerbate hypercalcemia, they were only used after parathyroidectomy in the current patient.

A low-salt and low-protein diet can be used to decrease urine volume in proportion to the reduction of solutes excreted in the urine.[24]

Management of lithium-induced hypercalcemia and hyperparathyroidism

If hypercalcemia is mild and PTH level is not elevated, it might be possible to discontinue lithium for 2–4 weeks. If calcium level then normalizes, an alternative mood stabilizer can be considered. Normalization of serum calcium is most likely to occur 1–4 weeks after lithium withdrawal in patients who have used lithium for no more than a few years[6] and is unlikely in patients who have received lithium for more than 10 years.[11] Other factors that affect serum calcium normalization include the underlying parathyroid gland pathology and mass, and the use of other drugs that affect calcium metabolism (e.g. thiazide diuretics).

Patients in whom lithium cannot be discontinued should be observed and should have their serum calcium levels monitored.

If PTH level is elevated, the diagnosis of hyperparathyroidism is established (Figures 1 and 2). Symptomatic patients with primary hyperparathyroidism should be treated with parathyroidectomy. Indications for a surgical intervention in asymptomatic patients with primary hyperparathyroidism are presented in Box 2.[25] Parathyroidectomy was justified in the patient presented here by the presence of severe hypercalcemia and renal calculi. The recommended surgical approach is exploration of all four parathyroid glands.[25] The role of preoperative localization of pathologic parathyroid glands in patients without prior surgery has not been established for sporadic primary hyperparathyroidism[25] or for lithium-associated hyperparathyroidism. Furthermore, in view of the increased incidence of glandular hyperplasia in patients with lithium-associated disease, the positive predictive value of preoperative localization is likely to be lower in patients with lithium-associated hyperparathyroidism than in those with sporadic hyperparathyroidism. Finally, a recent report recommended bilateral neck exploration in

Box 2 Indications for surgical intervention in asymptomatic patients with primary hyperparathyroidism.[25]

- Age <50 years
- Serum calcium level >0.25 mmol/l (>1 mg/dl) above upper limit of normal
- Bone density more than 2.5 standard deviations below that of a young normal adult at any skeletal site (e.g. spine, hip, forearm)
- Hypercalciuria (urinary calcium >400 mg/24 h)
- Creatinine clearance less than 30% of that of age-matched controls

patients with lithium-associated hyperparathyroidism, as intraoperative PTH level monitoring has a limited ability to predict curative parathyroidectomy in such patients.[12]

Treatment options for severe hypercalcemia in patients awaiting parathyroidectomy are shown in Box 3.

Box 3 Treatment options for severe hypercalcemia in patients awaiting parathyroidectomy.

- Volume expansion with intravenous isotonic saline. Volume expansion inhibits sodium reabsorption (which is coupled to calcium reabsorption; Figure 4) in the proximal convoluted tubule and the ascending loop of Henle, thereby increasing urinary calcium excretion. Required volumes range from 2 l to 6 l over 24 h, depending on the extent of dehydration and the cardiovascular status of the patient
- Loop diuretics (e.g. furosemide or bumetanide) to inhibit calcium reabsorption in the loop of Henle. These drugs should be used only in volume-replete patients. They were not used in the patient presented here because they can impair renal concentrating ability and worsen diabetes insipidus
- Intravenous bisphosphonates should be given if parathyroidectomy is delayed: 60 mg pamidronate intravenously over 2 h, or 4 mg of zoledronate intravenously over 15 min
- Surgical management of kidney stones to avoid obstruction and recurrent urinary tract infections. To minimize risk of new stone formation, stones should be removed after parathyroidectomy. Chronic suppressive antibiotic therapy might be indicated to prevent recurrence of infection in patients with residual stone disease
- The calcimimetic cinacalcet is approved for the treatment of secondary hyperparathyroidism and parathyroid carcinoma, but not for primary hyperparathyroidism. Although experience with cinacalcet in patients with lithium-associated hyperparathyroidism is very limited, this agent might be a therapeutic alternative in patients who are not candidates for surgery[26]

CONCLUSIONS

This case illustrates two metabolic complications associated with chronic lithium therapy—hypercalcemia and nephrogenic DI. Both conditions are unlikely to be reversible when lithium has been discontinued after chronic use.

It is unclear whether the patient developed hyperparathyroidism because of chronic lithium use or whether she had underlying hyperparathyroidism that was unmasked by lithium therapy. Measurement of calcium levels before initiation of lithium therapy would have helped to differentiate between these two possibilities. Hypercalcemia might have aggravated the nephrogenic DI, but, as DI persisted after parathyroidectomy, it was not the main cause.

The pathophysiology of hypercalcemia with lithium use is altered calcium sensing through an effect on CaSR signaling, and the unmasking or induction of hyperparathyroidism. That of nephrogenic DI is decreased density of ADH receptors, downregulation of aquaporin-2 channel expression, and tubular sclerosis. The exacerbation of hypercalcemia with nephrogenic DI, and that of DI with hypercalcemia, can be explained by the crosstalk between calcium and water handling, and the impact of the CaSR on countercurrent multiplication and possibly on aquaporin-2 channel expression. Lithium-associated hyperparathyroidism is managed in a manner similar to sporadic primary hyperparathyroidism. Nephrogenic DI is treated with amiloride (in patients on lithium), thiazides (after correction of hypercalcemia), and initiation of a low-protein, low-sodium diet.

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Competing interests
EM Brown has declared associations with Amgen. See the article online for full details of the relationship. The other authors declared they have no competing interests.

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