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**Case Report**

# Three Patients with Lithium-Associated Hyperparathyroidism: Literature Review Regarding Medical and Surgical Management

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**Keywords**

Lithium · Secondary hyperparathyroidism · Tertiary hyperparathyroidism · Hypercalcemia · Parathyroid hormone levels · Calcimimetics · Parathyroidectomy

**Abstract**

Lithium (Li) carbonate has been established as a mood stabilizer and an efficacious treatment for bipolar disorder since its discovery by Dr. John Cade in 1948. Li interacts significantly with organ systems and endocrine pathways. One of the most challenging side effects of Li to manage is its effect on the parathyroid glands. Dysregulation of parathyroid signaling due to Li results in hypercalcemia due to increased vitamin $D_3$ generation, increased calcium absorption from the gut, and bone resorption, occasionally resulting in concomitant hypercalciuria.



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However, hypercalciuria is not a definitive feature for hyperparathyroidism, and normal calcium excretion might be seen in these patients. Hypercalcemia may also result from volume contraction and decreased renal clearance, which are commonly seen in these patients. Anatomically the parathyroid abnormalities can present as single or multiglandular disease. We report 3 cases where the patients developed multiple side effects of Li therapy as well as hypercalcemia due to hyperparathyroidism. The literature is reviewed with regard to medical and surgical management of Li-associated hyperparathyroidism in the context of these 3 presented cases.



## Introduction

Lithium (Li) carbonate was discovered in 1948 by Dr. John Cade [1], and came into full clinical use in the 1980s as a mood stabilizer. Its mechanism of action as a mood stabilizer remains controversial, but some suggest that Li crosses the blood-brain barrier and inhibits the synthesis of norepinephrine and serotonin, thereby regulating mood [2]. From the beginning of its use, it was recognized that Li (as an elemental monovalent cation) had some structural similarity to calcium in interacting with protein receptors and that this posed a risk for side effects. Renal side effects are generally mediated by Li binding to calcium-sensing receptors (CaSR) in the ascending thick loop of Henle [3]. This directly induces polyuria in a fashion similar to hypercalcemia. Long-term Li use can cause renal failure and a phenomenon called creatinine creep where serum creatinine rises with long periods of Li administration [4, 5]. Li can also cause hypothyroidism, which can occur through inhibition of thyroxine (T4) synthesis and inhibition of thyroxine conversion to liothyronine (T3) [6]. Hyperthyroidism has been reported in association with Li as well usually necessitating discontinuation of the agent [7].

One of the most complex complications of Li therapy is parathyroid dysfunction that occurs due to adenoma formation or hyperplasia of the parathyroid gland(s) under the trophic influence of CaSR stimulation by Li [8]. Li-associated hyperparathyroidism (LAH) presents with single adenomas in 45–80% of cases and with generalized hyperplasia in the other 20–55% of cases, with varying percentages in different series [8–13]. When conservative management fails or is not possible, there is a 60–80% cure rate with surgery [11, 13, 14]. Parathyroidectomy may be curative, but in some cases residual disease due to hyperplasia of the remaining tissue may necessitate long-term medical therapy with calcimimetics agents like cinacalcet [12, 13]. We discuss 3 patients who developed several of the systemic complications of Li therapy as well as the medical and surgical challenges of LAH management.

## Case Reports

*Patient 1*

Patient 1 is a 53-year-old Hispanic female diagnosed with schizoaffective disorder at the age of 13 and on Li therapy for 40 years. She had been on 600 mg of Li that was increased to 1,200 mg just prior to September 2016. She at that point became Li toxic (level of 2.99 mg/day) and hypercalcemic (1.59 mmol/L). She was hospitalized and treated with hydration

and hemodialysis for removal of the excess Li. Her calcium levels remained at 10.5–11.8 mg/dL. Lithium was discontinued in September 2016, and her bipolar medication was switched to lurasidone. Since her Li was stopped, her serum creatinine had remained somewhat elevated at a range of 1.1–1.3 mg/dL, with GFRs between 45 and 50 mL/min/1.73 m$^2$ (Fig. 1). Also noted was some mild to moderate proteinuria (Table 1). The 25-hydroxyvitamin D levels were measured around 31 ng/mL (normal: 20–50 ng/mL).

Despite the discontinuation of Li, the patient had persistence of the hypercalcemia. She also developed Li-associated diabetes insipidus, diagnosed with a serum sodium level of 164 meq/L during an inpatient hospitalization, which was subsequently managed with increased water intake. In evaluating her hypercalcemia, she was diagnosed with hyperparathyroidism with a PTH level of 247 pg/mL (normal range 11–51 pg/mL). As an attempt at localization, a nuclear medicine sestamibi parathyroid scan was performed and showed a single area of focal hyperintensity in the right lower thyroid pole consistent with a parathyroid adenoma. A CT parathyroid scan showed a 5-mm left parathyroid focus without any right-sided glands. Of note, she also had a multinodular goiter with a large 4.7-cm right thyroid nodule and fine needle aspiration biopsy showed benign findings. The larger size of this nodule increases the risk of false-negative biopsies [15], and thus surgical removal of this nodule was considered.

She was started on cinacalcet with the hope that discontinuation of the Li could be enough to reverse its effects on the parathyroid glands but it was stopped 1 month after initiation. She then suffered a fall and a left ulnar fracture in May 2017. Ultimately, the control of the parathyroid disease using cinacalcet was not optimal. She was very lethargic and symptomatic from both her psychiatric illness and her parathyroid disease. Given these issues and the persistence of hyperparathyroidism, surgical management was recommended. Patient 1 then underwent removal of the aforementioned thyroid nodule along with a subtotal parathyroidectomy with resection of the right superior, right inferior, left inferior, and 2/3 of the left superior parathyroid glands during September 2017. The result has been a dramatic decrease in serum calcium to 9.6 mg/dL and PTH to 13 pg/mL. Her serum creatinine remained stable at 1.3 mg/dL thereafter (Fig. 1).

*Patient 2*

Patient 2 is a 55-year-old Middle-Eastern female who was diagnosed with bipolar disorder and had been treated with Li for more than 30 years. Her Li dose was initially 600 mg twice a day (total dose 1,200 mg) and was started in 1996. The Li dose was then decreased to 300 mg at a.m. and 450 mg at bedtime (total dose 750 mg). Lamotrigine was added as a supplemental medicine to treat bipolar disorder with the goal of eventually tapering Li to the lowest effective dose. She also had stage IIIb chronic kidney disease (CKD) with a serum creatinine ranging between 1.7 and 2.2 (GFR 26–31 mL/min/1.73 m$^2$). This patient had moderate proteinuria and was also diagnosed with nephrogenic diabetes insipidus. Additionally, she developed hypothyroidism, requiring the use of replacement levothyroxine to normalize her TSH. The diagnosis of hyperparathyroidism was made in 2016, after 29 years of Li therapy, with the finding of an elevated serum calcium level of 10.9 mg/dL, a ionized calcium of 1.35 mmol/L, and a PTH level of 134 pg/mL. The 25-hydroxyvitamin D level was borderline to normal at 25–30 ng/mL and the 1,25-dihydroxy-vitamin D level was also normal at 46.3 pg/mL.

Parathyroid sestamibi scan was performed in anticipation of a potential surgical intervention. It showed a discrete uptake from a probable parathyroid adenoma in the right mid

thyroid lobe. The general trend of serum Ca and PTH improved within a year after the Li dose was reduced (Fig. 2). Patient 2's serum calcium and PTH levels normalized in about 3 months after decreasing the dose of Li without the need for cinacalcet or surgery. She is likely in the subset of patients who will have improvement of LAH with withdrawal of the offending drug alone.

*Patient 3*

Patient 3 is a 65-year-old Hispanic female who was diagnosed with bipolar disorder and had been treated with Li for 25 years. Her Li dose was 900 mg daily at night. This was tapered off in March 2013 due to her developing hyperparathyroidism. She was then started on Depakote and valproic acid, with good control of her bipolar symptoms. After the cessation of Li, the patient's serum creatinine was noted to range between 1.2 and 1.6 mg/dL (eGFR 45–50 mL/min/1.73 $m^2$). Proteinuria was microscopic but present at 130 mg/g Cr, and albuminuria was not detected (<30 mg/g Cr). 25-Hydroxyvitamin D levels were in the normal range (41 ng/mL, with a normal range of 30–80 ng/mL). Hypernatremia, polyuria, and polydipsia were noted with serum osmolality at 294 mosm/L, and urine osmolality at 245 mosm/L. The diagnosis of nephrogenic diabetes insipidus due to Li was made given these findings.

A multinodular goiter was noted with normal thyroid function tests. A fine needle aspiration did not show any evidence of malignancy from the dominant thyroid nodule, which was 1.3 cm in size in the largest dimension. Hypercalcemia with values ranging between 10.6 and 10.9 mg/dL and ionized calcium of 1.36 mmol/L were also noted. PTH was only mildly elevated at 80–120 ng/mL. This was in the presence of hypercalcemia, which was inappropriate. Sestamibi parathyroid imaging revealed focused parathyroid uptake near the right thyroid nodule. Given her persistent hyperparathyroidism after stopping Li, she was managed with a subtotal parathyroidectomy in April 2015. This resulted in normalization of serum calcium and PTH levels, though with persistence of CKD from Li-induced tubular damage. Her PTH levels rose slowly for a bit more than a year (Fig. 3). Following the operation, the reduction in serum calcium was clear and long-lasting, but given the slight increase in the parathyroid hormone levels only a year postoperatively, there is concern for residual disease. The patient is being monitored for any recurrence of hypercalcemia that may necessitate treatment with calcimimetics or surgical reoperation.

## Review of the Literature: Medical versus Surgical Management of LAH

LAH is observed in a significant portion of patients receiving chronic Li therapy. The manifestations are multifaceted, and firm treatment guidelines are sparse for this condition. The decision to operate or to maintain a patient on medical therapy with LAH is challenging, because there are as of yet no firm guidelines. In most cases, the treating physicians follow the established guidelines for the treatment of primary hyperparathyroidism to approach the LAH. One area that distinguishes LAH from primary hyperparathyroidism is the reversibility of pathology with stopping Li. While both hyperparathyroidism's hypercalcemia may cause renal injury, in LAH Li causes hypercalcemia and directly damages renal tubules.

Calcimimetic therapy can be considered after reversing hypovolemia in patients with LAH, though these agents may not work in all patients. However, this is an area of interest and

more research is required to investigate this approach in more depth. Further, the presentation of LAH can be variable, and LAH can subside or improve on its own though in some patients the time to this improvement varies [16]. It has also been noted that some cases of LAH are asymptomatic with borderline normal calcium and PTH levels. This also includes patients with normal levels of urinary calcium excretion as opposed to the expected hypercalciuria [16].

Another important component of LAH is the increased risk of CKD with long-term Li use, as noted in the reported cases as well. Long-term Li can lead to CKD, which in turn can contribute to the development of vitamin D deficiency and hyperparathyroidism. However, the secondary hyperparathyroidism with CKD is usually seen in the more advanced stages of CKD (late stage 4 and stage 5), is associated with low to normal calcium levels (as opposed to hypercalcemia seen in LAH). Considering the normal vitamin D levels, hypercalcemia and CKD stage 3 to early 4 in our cases, it seems that LAH was the major contributor. Even the timing of surgery in more severe cases remains controversial as Skandarajah et al. [12] notes. The likely reason for this is that most published data comes from several case series studies (the largest of which presents 71 patients) where the parathyroid disease may have been due to diverse etiologies [11, 12]. These series also cannot provide the statistical tools to compare outcomes in differently treated arms [12].

The link between sustained Li use and hyperparathyroidism has been repeatedly reported in the literature [8, 12, 13]. Though the literature makes it clear that while stopping Li improves LAH, the risk of relapse of manic symptoms increases up to 28-fold after stopping Li therapy [17]. There are other disagreements about the diagnosis, medical, and surgical management of LAH. This is likely because most of the recommendations are based on case reports, retrospective data, and expert opinion, rather than clinical trials [4, 7, 12, 13, 17–22]. This requires that diagnosis and treatment decisions be individualized to a patient's particular situation [17, 20, 22].

If a patient's medical team has recommended surgery, imaging assistance for surgical planning may be equivocal. Given the high rate of multiglandular parathyroid disease (MGD) (20–55%) [8–13], it is important to note that the normally high sensitivity of sestamibi imaging in detecting parathyroid adenomas goes down with concomitant thyroid abnormalities and in MGD patients [17, 23, 24]. According to Nichols et al. [25, 26], sestamibi imaging sensitivity is 61% for MGD versus 97% for single-gland parathyroid disease (SGD). Specificity is also decreased for MGD (84%) compared to SGD (93%) [25–27].

Parathyroid ultrasound as an alternate modality has the issue of a low sensitivity even in patients with uncomplicated SGD (at 40%). Alternative nuclear medicine studies ($^{18}$F-fluorocholine PET/CT) are available and both show 94 and 88% sensitivity, respectively [28]. However, they have not been directly tested for these parameters in LAH, particularly in patients with MGD [28].

Another emerging tool is the employment of 4D CT scans, which look at changes in enhancement as well as anatomical structure they can localize the correct quadrant of the parathyroid adenoma with a sensitivity of 76–80% and a specificity of 80–90% [29]. Despite these imaging advances, some patients with LAH still have equivocal scintillography and 4D CT scan findings. Neck exploration may be necessary in many cases where nuclear medicine parathyroid imaging is equivocal [12, 17, 22].

The role for calcimimetics in ameliorating hypercalcemia and elevated PTH levels in LAH has also been graded as a grade C recommendation [17]. Medical versus surgical management also remains controversial. Umashankar et al. [20] suggested that a surgical approach is warranted in most patients and that medical control is an option for only a few patients who received short-term Li therapy. LAH is noted to be common among Li users with cross-sectional studies showing hypercalcemia in 15% of Li-treated patients [19]. It has been suggested that asymptomatic or mildly hypercalcemic patients are better suited to medical therapy, where more severe hypercalcemia and hyperparathyroidism warrant surgical therapy [21]. In patients with more advanced CKD, correcting the underlying vitamin D deficiency and the volume status might improve the condition and decrease the need for parathyroidectomy. Care needs to be employed in utilizing the surgical approach, due to the heterogeneous types of lesions noted in LAH. Estimates for prevalence of MGD range from 20% up to 55% in different series [9, 10]. It has also been noted in studies that patients with SGD tend to be easier to control and to remain normocalcemic after parathyroidectomy. The disease mechanism of Li binding to CaSR would be expected to affect multiple glands [8]. The nearly 20–42% recurrence rate of LAH following parathyroidectomy quoted by different studies suggest that some SGD cases with recurrence are actually undiagnosed MGD [11, 14]. MGD is also predictably associated with longer duration of Li therapy [30].

Several tools including 4D CT scan and intraoperative PTH 5 min following excision monitoring have been developed in order to minimize chances of missing a hyperactive gland. The failure of the intraoperative 5-min post excision PTH test to drop by 35% from baseline would indicate a high likelihood of the presence of another hyperactive parathyroid gland [31]. The risk of missing an active gland in MGD is high and biochemical monitoring needs to be undertaken to avoid this. This agrees with Qiu et al. [32] who found that total parathyroidectomies were more efficacious than partial parathyroidectomies or partial parathyroidectomies with auto transplantation.

The three cases we present in this series show the spectrum of disease in LAH and the different approaches that can be used in line with the literature [21, 33]. The best evidence currently indicates that stopping Li with any hypercalcemia or if a high PTH is present. Stopping Li can decrease hypercalcemia and in some cases can lead to the control of parathyroid disease in some patients on long-term Li therapy [21]. The risk of manic symptom relapse after stopping Li should be noted and patients should be appropriately counseled [17]. The renal and endocrine effects of Li can last for months to years after cessation of therapy. A combination of sestamibi scanning, $^{18}$F-fluorocholine PET, and 4D CT can help localize the side of the neck and quadrant of parathyroid activity preoperative, while intraoperative PTH sampling can help identify hyperplastic parathyroid tissue.

SGD is roughly as common as MGD, but SGD is more easily treated with less recurrence than MGD. Medical therapy with cinacalcet may be helpful in controlling hypercalcemia and decreasing PTH levels in patients who have been diagnosed with LAH early on while waiting for the subset of patients who will resolve with cessation of therapy to improve [34]. If no improvement is noted 1–2 years after cessation of therapy operative planning may be undertaken with appropriate imaging studies mentioned above. For SGD and even in some MGD, some authors advocate minimally invasive parathyroid surgery. Other studies suggest total parathyroidectomy as superior to subtotal parathyroidectomy or total parathyroidectomy with auto-transplantation [32]. While this makes sense with the recurrence risks of MGD,

complete parathyroidectomy is a complex surgery that also risks permanent hypoparathyroidism. Finally, medical therapy with cinacalcet may also have a role in patients who show recurrence after a subtotal parathyroidectomy or parathyroidectomy with auto-transplantation while evaluation is pending for reoperation. More work remains to be done in terms of prospective trials to define the best diagnostic strategies, uses of medical and surgical therapies in the multifaceted and nuanced management of this disease.

## Statement of Ethics

This research is determined to not contain human subjects research material after consultation with UCLA IRB Committee and was not required to present an IRB. As such it is in harmony with the guidelines of the World Medical Association Declaration of Helsinki. The subjects have given documented consent for publication of this data and consent to publish their case anonymously. No images are published and no identifying information is disclosed. Patients are identified by numbers and not by their real names.

## Disclosure Statement

The authors have no conflict of interest as pertains to this work.

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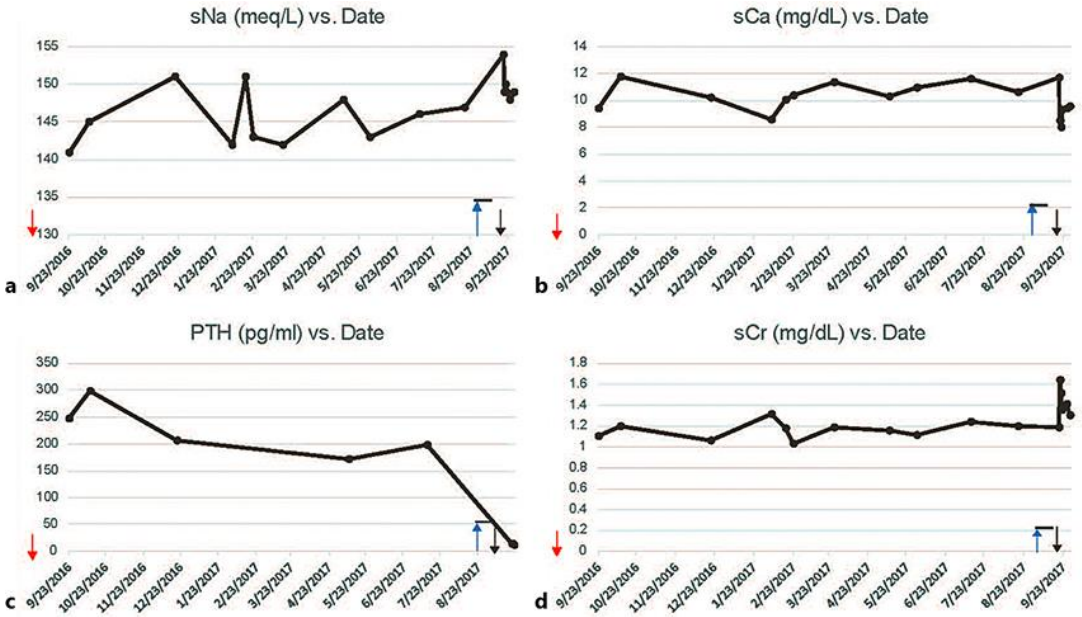


**Fig. 1.** Patient 1. **a** Graph of serum sodium (sNa, in meq/L) versus date. **b** Graph of serum calcium (sCa, in mg/dL) versus date. **c** Graph of parathyroid hormone (PTH, in pg/mL) vs. date. **d** Graph of serum creatinine (sCr, in mg/dL) versus date. The blue arrow and the line indicate the duration of cinacalcet therapy; the red arrow indicates cessation of Li during September 2016; the black arrow indicates the date of subtotal parathyroidectomy in September 2017.

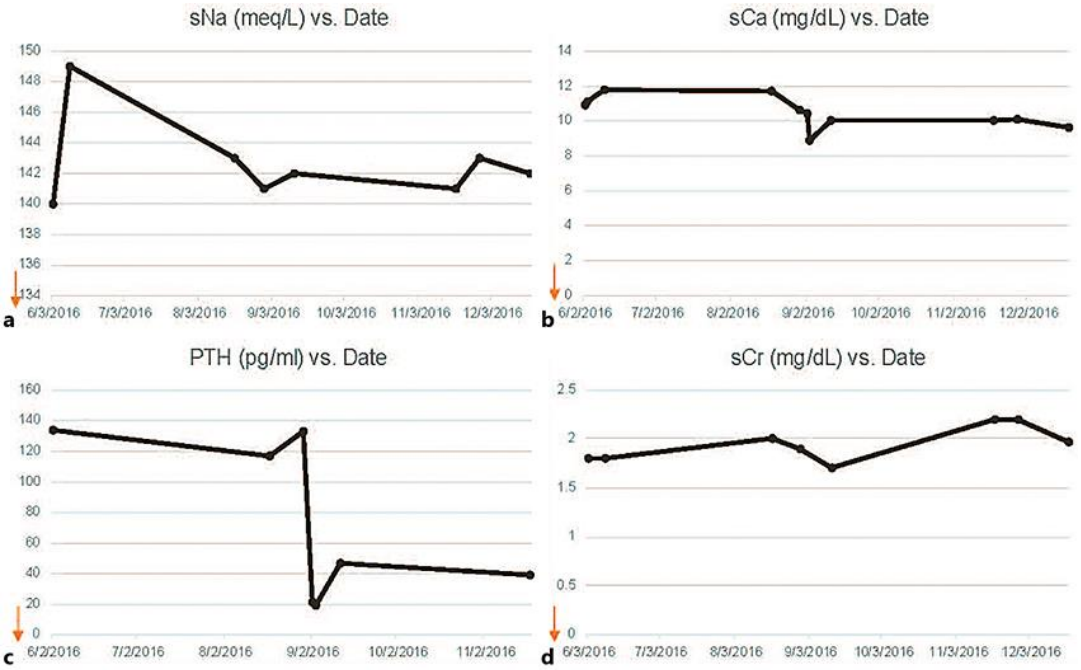


**Fig. 2.** Patient 2. **a** Graph of serum sodium (sNa, in meq/L) versus date. **b** Graph of serum calcium (sCa, in mg/dL) versus date. **c** Graph of parathyroid hormone (PTH, in pg/mL) versus date. **d** Graph of serum creatinine (sCr, in mg/dL) versus date. The orange arrow indicates a decrease in Li dose from 1,200 mg total daily dose to 750 mg total daily dose before data obtained (patient maintained on this dose throughout).

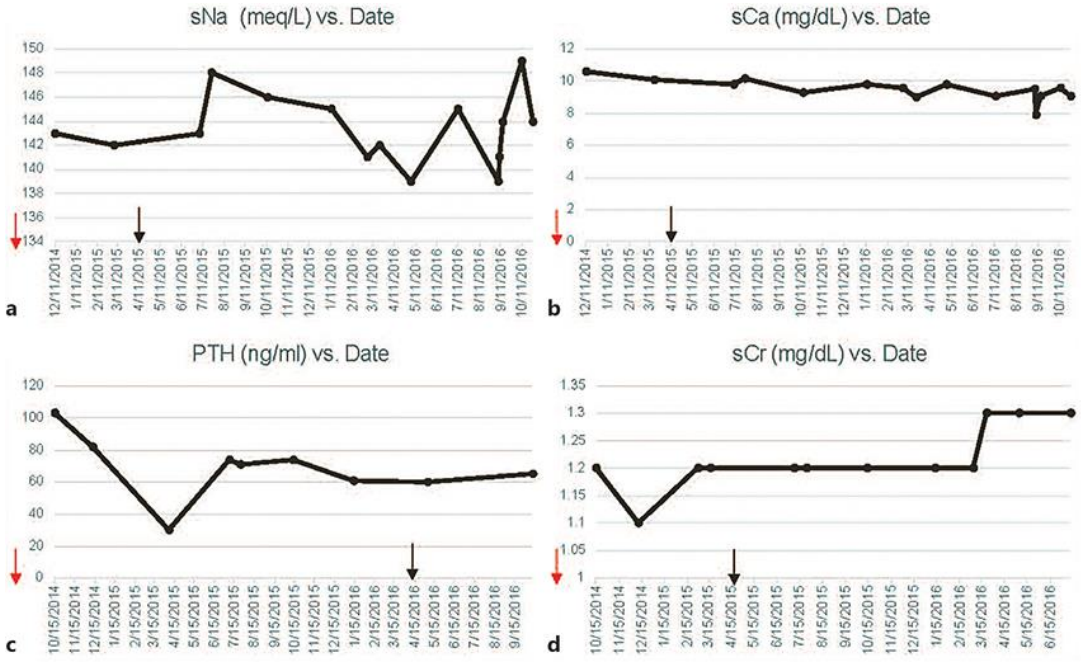


**Fig. 3.** Patient 3. **a** Graph of serum sodium (sNa, in meq/L) versus date. **b** Graph of serum calcium (sCa, in mg/dL) versus date. **c** Graph of parathyroid hormone (PTH, in pg/mL) versus date. **d** Graph of serum creatinine (sCr, in mg/dL) versus date. The red arrow indicates cessation of Li before data set obtained (March 2013); the black arrow indicates subtotal parathyroidectomy (April 2015).

**Table 1.** Comparing patients 1, 2, and 3

| Pat. | G | Tox | Eth. | Age | sNa range | sCa range | PTH range | sCr range | Prot | Alb | Thy | DI? | CinC? | Surg? | Li | LOT | TPH | TTS | NM PT imaging |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | F | Y | H | 53 | 141–151 | 10.3–11.8 | 171–299 | 1.03–1.31 | 0.2–0.6 | <30 | Nod | yes, p | Y | Y | S | 40 yr | 12 | 12 | RL PTA |
| 2 | F | N | ME | 55 | 140–149 | 9.6–11.8 | 39–134 | 1.7–2.2 | 1.4 | 788 | Hypo | yes, p | N | N | D | 30 yr | 3 | n/a | UT RM thyroid |
| 3 | F | N | H | 65 | 135–149 | 7.9–10.6 | 30–103 | 1.1–1.4 | 0.13 | <30 | Nod | yes, p | N | Y | S | 25 yr | 24 | 24 | UT R thyroid |

Alb, albumin (albuminuria in mg/g creatinine); CinC, cinacalcet use; D, decreased dose; DI, diabetes insipidus – all cases nephrogenic; Eth, ethnicity; F, female; G, gender; H, Hispanic; Hypo, hypothyroid; Li, Lithium; LOT, length of Li therapy (in years); ME, Middle Eastern; N, no; Nod, thyroid nodule; NM, nuclear medicine; p, partial; Pat, patient; Prot, protein (proteinuria in g/g creatinine); PT, parathyroid; PTA, parathyroid adenoma; PTH, parathyroid hormone (in pg/mL); R, right; RM, right mid; RL, right lower; sCa, serum calcium (mg/dL); sCr, serum creatinine (in mg/dL); sNa, serum sodium (in meq/L); S, stopped medication; Surg, surgery; Thy, thyroid pathology; Tox, acute toxicity; TPH, time with persistent hypercalcemia after discontinuation of Li therapy (in months); TTS, time waited until patient got surgery after discontinuation of Li therapy (in months); UT, uptake; Y, yes; Yr, years.