CASE REPORT

Lithium-associated hyperparathyroidism: report of four cases and review of the literature

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Abstract

Context: Lithium-associated hyperparathyroidism (LAH) was first described in 1973 but many issues remain in question regarding the pathophysiology as well as the appropriate management of this condition.

Objective: Report of four new cases and review of the literature.

Results: We describe two males and two females, treated for more than 10 years with lithium due to bipolar disorder, who developed LAH. All underwent parathyroidectomy. In three cases (75%), pathology revealed multiglandular disease, with hyperplasia or two parathyroid adenomas. We observed a cure status in three (75%) of the operated patients. The fourth patient had a residual disease, but had controlled hypercalcemia under the calcimimetic drug cinacalcet. We also observed the association of LAH with incidental papillary thyroid carcinoma in two patients. Review of the literature identified a higher prevalence of LAH in women than men (four out of one) and a controversy in regard to the prevalence of multiglandular disease. As a result, there is no consensus regarding the preferred surgical procedure. The use of cinacalcet as an effective treatment of LAH was previously described in only five cases.

Conclusion: In our view, there are apparently two different mechanisms leading to LAH: exacerbation of a pre-existing state of hyperparathyroidism and multiglandular disease. For uncontrolled hypercalcemia, parathyroidectomy is recommended. The issue of routine four-gland exploration and subtotal parathyroidectomy versus intraoperative PTH-determination-guided excision of enlarged glands is still unresolved. The use of the recently developed calcimimetics may offer an alternative to patients who are not candidates for surgery.

European Journal of Endocrinology 160 317–323

Introduction

Lithium is a potent antidepressant agent proven to be highly effective for bipolar disorders since 1949 (1). Lithium-associated hyperparathyroidism (LAH) was first described in 1973 (2) but many issues still remain unclear regarding this condition. It is unclear whether lithium initiates the disease or uncovers an underlying state of hyperparathyroidism (HPT). Moreover, it is unknown whether LAH causes four-gland hyperplasia or promotes the growth of pre-existing parathyroid adenomas (PTA). It has even been suggested that patients treated with lithium present more often with multiple PTAs than the general population. At our institution, the Hadassah-Hebrew University Medical Centers in Jerusalem, patients with HPT meeting criteria for parathyroid surgery (3) are managed according to a simple algorithm described in Fig. 1; the preoperative evaluation includes a neck-ultrasound and a sestamibi scan. If imaging studies localize a single adenoma, minimal invasive parathyroidectomy is performed. Four-gland exploration is

applied in cases of failure of intraoperative PTH to fall under 50% of the baseline level or in cases of negative preoperative localization. We have no particular considerations in cases of patients with LAH. The following is a brief discussion of four such patients encountered and treated during the last 2 years at our institution.

Patient 1

A 59-year-old male was treated with lithium for a bipolar disorder for almost 40 years. HPT was diagnosed 3 years after the discontinuation of lithium, on the basis of routinely performed blood and urine tests: blood calcium 10.8 mg/dl (8–10.5); urinary calcium 768 mg/day ($N < 300$ mg/day); PTH 18.7 pmol/l (1.26–6.84). A bone mineral densitometry (BMD) showed reduced T-score: -1.8 (neck of femur), -1.1 (spine), and -2.4 (forearm). Mechxysanutyl isonibile (MIBI) scan suggested a right lower PTA and ultrasonography verified the presence of a 10 mm right lower PTA. However,

Figure 1 Algorithm of management of patients with hyperparathyroidism at the Hadassah-Hebrew University Medical Center, Jerusalem.

because intraoperative PTH failed to fall below the required 50% from baseline, further neck exploration was performed. Eventually, three enlarged parathyroid glands weighing 100, 1300, and 1300 mg were removed. The fourth gland looked macroscopically normal in size and appearance and was left in place. Intraoperative PTH levels dropped from 23.4 to 4.4 pmol/l (1.26–6.84). Postoperatively, the patient became normocalcemic and stayed so for the last 2 years of follow-up. Currently, the patient is doing well without the need for lithium therapy. Pathology reported that all the glands removed were hyperplastic parathyroid glands.

Patient 2

A 71-year-old male suffering from bipolar disease for many years responding well to lithium therapy. His mental state deteriorated acutely and required hospitalization in the department of psychiatry. His blood calcium level was found to be 12.5 mg/dl (8–10) and intensive therapy was undertaken to lower his hypercalcemia. As lithium therapy was essential and could not be discontinued, a preoperative workup was performed. Ultrasonography failed to detect any enlarged parathyroid glands. A MIBI scan detected retention of isotope at the lower pole of the left thyroid

lobe and another suspicious area of retention at the right thyroid lobe.

At exploration, a left lower parathyroid adenoma measuring $18 \times 7 \times 5$ mm was excised. The left upper parathyroid was only mildly enlarged and was left in place. Another right PTA $17 \times 7 \times 5$ mm was excised. Intraoperative PTH levels were 47.7 pmol/l (1.26–6.84) before excision and dropped to 4.8 pmol/l post-excision. During a follow-up period of 22 months, normocalcemia is maintained and the patient's psychiatric condition is stable.

Patient 3

A 65-year-old female with a bipolar disorder treated with lithium for close to 40 years. The patient was hospitalized for severe hypercalcemia of up to 13.3 mg/dl and with elevated PTH of 17.8 pmol/l (1.26–6.84) and was treated accordingly. Due to the severe and resistant hypercalcemia, lithium was discontinued. After a period of 3 months without significant improvement, the patient was referred to surgery. Preoperative evaluation revealed a multinodular goiter (MNG) on ultrasonography and a non-informative MIBI scan. Therefore, it was decided to perform a four-gland parathyroid exploration.

On the right, only the lower parathyroid gland was identified. It was enlarged (150 mg) and was removed. Also removed was the upper left parathyroid gland (100 mg). No further parathyroid glands were detected and the intraoperative PTH level remained elevated (17 pmol/l pre- and post-resection). Thus, a subtotal thyroidectomy was undertaken with PTH levels dropping to 9.3 pmol/l. Pathology reported two enlarged parathyroid glands and no parathyroid tissue within the thyroid. However, three microscopic foci (0.1–0.2 mm each) of papillary thyroid carcinoma (PTC) were reported in both thyroid lobes. It was decided to start a TSH-suppressive eltroxin dose without radioactive iodine therapy. During the year after the surgery, the patient had mildly elevated serum calcium levels up to 10.6 mg/dl (8–10.5) with mildly elevated serum PTH levels up to 12 pmol/l (1.26–6.84), normal urinary calcium, as well as normal BMD. As her psychiatric condition deteriorated and resisted to all therapeutic attempts, lithium therapy had to be resumed. At a dose of 600 mg/day, her serum calcium levels raised to 11.6 mg/dl, and PTH levels to 21 pmol/l (1.26–6.84). Neck ultrasound showed a suspected ectopic finding compatible with PTA at the sternal notch, and a MIBI scan showed an increased signal in the mentioned area as well as in the left upper neck. The patient refused further surgery and therefore a therapeutic trial with daily dose of cinacalcet 30 mg was initiated. Under this treatment, her serum calcium levels were normalized to 10 mg/dl and PTH levels were reduced to 18.9 pmol/l. Later on, lithium was discontinued because of a severe

psoriatic skin rash; the patient continued to take cinacalcet at the same dose for two additional months, reaching calcium levels of 9.2 mg/dl without changes in PTH levels. On follow-up, her psychiatric conditions stabilized under combined antipsychotic therapy, and she remained stable enough to withhold further neck exploration, despite the presence of two suspected PTA. There was no deterioration in her clinical or laboratory status after the withdrawal of cinacalcet.

Patient 4

A 64-year-old woman treated with lithium for 12 years due to severe depression. The drug was discontinued because of elevated calcium levels of up to 10.2 mg/dl (8–10) and PTH levels reaching 14.47 pmol/l (1.26–6.84). Moreover, the patient complained of heavy thirst and polyuria (up to 7 liters a day) and was diagnosed as suffering from nephrogenic diabetes insipidus after a water-deprivation test showed increasing blood osmolality up to 308 mosm/l without any response to the injection of s.c. desmopressin. Six years after the discontinuation of lithium, the patient had severe osteoporosis, with calcium levels of 10.32 mg/dl (8–10), PTH levels of 26.8 pmol/l (1.26–6.84), and severe hypercalciuria (600 mg/day). On the preoperative evaluation, neck ultrasonography revealed thyroid MNG and a suspected right upper PTA. The MIBI scan was not informative. At surgery, a right upper PTA (13×8 mm) was resected, and intraoperative PTH levels dropped to 5 pmol/l (1.26–6.84). However, a mildly enlarged and tough lymph node at the anterior neck, which was removed, was revealed to harbor PTC. Thus, the patient underwent total thyroidectomy, which identified a tumor of 10×10 mm in the left thyroid lobe, without vascular invasion, and two microscopic foci of PTC in the right thyroid lobe (1 and 2 mm). The pathologic examination reported one normal parathyroid gland. The patient received 150 mci of radioactive iodine, and was started on a TSH-suppressive dose of eltroxin. After surgery, the patient had persistent hypocalcemia that responded well to calcium and vitamin D3 supplements. On follow-up, the patient stabilized at low-normal calcium (7.6–8.4 mg/dl) and PTH (3.1 pmol/l) levels (Table 1).

Discussion

Since the first case report of lithium-associated HPT (2), a search in the PubMed database came up with 111 entries, describing more than 140 cases of LAH, in small series (Table 2) or case reports. Of note, the spectrum of lithium-induced calcium homeostasis disorders is wide and includes cases of overt HPT, as well as cases of hypercalcemia without elevated PTH levels or elevated PTH without hypercalcemia (4, 5). The prevalence of

Table 1 Lithium-associated hyperparathyroidism in four patients.

	Sex, age (year)	Duration of lithium therapy (years)	Withdrawal of lithium prior to diagnosis (years)	Associated findings	Results of pathology after surgery	Associated thyroid disease
Patient 1	M, 59	>40	3	Hypercalciuria Osteoporosis	Three hyperplastic glands without adenoma	No
Patient 2	M, 71	>10	0	–	Two PTA (right and left)	No
Patient 3	F, 65	>40	0	Normocalciuria	Two PTA (right and left)	Three microscopic foci of thyroid papillary carcinoma
Patient 4	F, 63	12	5	No osteoporosis Osteoporosis Hypercalciuria	One PTA (right)	Macroscopic papillary carcinoma of thyroid with two contralateral microscopic foci

Table 2 Review of publications describing lithium-associated hyperparathyroidism (LAH) with pathological results (*N*= numbers of cases).

Name, year	<i>N</i>	Women (%); mean age in years (range)	Mean duration/range of duration of lithium therapy in years	Discontinuation of lithium prior to surgery	Parathyroid pathology
Carchman <i>et al.</i> (2008) (18)	16	81%; (54 ± 8)	3–22 years	In eight patients (50%). 0.5–10 years	Single adenoma: 75% Two adenomas: 6.25% ≥ Three glands hyper- plasia: 12.5% Normal: 6.25%
Hundley <i>et al.</i> (2005) (19)	12	83%; 54 (36–74)	Chronic or long term without further specification in 50% of cases, but > 10 years in 50%	In four patients (33.3%). 5 months to 4.5 years	Single adenoma: 50% Double adenoma: 25% Hyperplasia: 25%
Awad <i>et al.</i> (2003) (6)	15	73%; 58 ± 8 (34–74)	10.7 ± 6 (2–24)		Single adenoma: 73% Double adenoma: 20% Hyperplasia: 7%
Abdullah <i>et al.</i> (1999) (20)	11	82%; 65 (46–84)	≥ 2 years	No	Single adenoma: 55% Double adenoma: 27% Hyperplasia: 18%
Bendz <i>et al.</i> (1996) (7)	8	87.5%; 64 ± 3.6 (51–78)	≥ 15 years		Single adenoma: 37.5% Double adenoma: 25% Hyperplasia: 37.5%
Ananth <i>et al.</i> (1983) (29)	17 ^a	82%; 44 (30–70)	1 day to 6 years		Single adenoma: 64% (no data in six patients)

^aReport of 3 new cases and review of 14 previous cases.

LAH is estimated to range from 4.3% (6) to 6.3% (7) and is higher than the overall prevalence of HPT in the general population (1–4/1000) (8). This higher prevalence might be biased by a more stringent screening in patients treated with lithium, thus including cases of fortuitous diagnosis of PTA in the setting of concomitant use of lithium. Our description of four new cases and the review of the literature underscore some important and debatable issues.

The higher prevalence of LAH in women

According to the numbers described in most large series (Table 2), the estimated female to male ratio is 4/1. This is consistent with the higher prevalence of HPT in women (three out of one) in general, especially in the post-menopausal age group, with a female prevalence estimated to be ≥ 3.4% (9). Interestingly, there is no

gender ratio in the occurrence of bipolar disease and it does not seem there are gender differences in regard to the use of pharmacological drugs for this disorder (10).

Mechanism of action of lithium on parathyroid cells

It is still unclear whether lithium initiates HPT or promotes an underlying subclinical state of HPT. It was shown that lithium causes a shift in the inhibitory set point for PTH secretion to a higher serum calcium concentration (11), which later suggested that lithium antagonizes the calcium-sensing receptor (CASR) (12) resulting in an increase in the threshold level of calcium required for suppression of serum PTH output by the parathyroids. This theory is further validated by the fact that many patients with LAH have inappropriately low-normal urinary calcium excretion (5, 13), as expected

in cases of inhibition of the CASR which is localized in parathyroid chief cells and the renal thick ascending limb (12). Indeed, inhibition of the CASR is illustrated by the typical clinical syndrome of familial hypocalcaemic hypercalcaemia (FHH) (14). The CASR is a membrane G-protein-coupled receptor (GPCR), mainly activated by polyvalent cations, which cause a cascade of intracellular molecular pathways, leading to the inhibition of PTH release (15). Lithium is capable to activate GPCRs, and to induce phosphorylation of protein kinase C (16), a key factor in the intracellular reactions usually induced by the activation of the CASR; as a monovalent cation, lithium might be thought to be a weak activator of the CASR. However, lithium apparently also interferes with other usual intracellular reactions observed in cases of activation of the CASR, eventually leading to an inactivation of the CASR. One possibility to explain this paradoxical fact is illustrated on Fig. 2: lithium interferes with the intracellular production of inositol triphosphate (IP3), via a specific inhibition of the enzyme inositol monophosphatase (IMPase) (16). The final effect of lithium on parathyroid chief cells might be the result of a balance between a weak activation at the level of the CASR and a stronger inhibition of intracellular pathways at the level of the IMPase. This topic deserves further studies to understand the exact mechanism of action of lithium on parathyroid cells, which may further explain the wide range of clinical and laboratory features observed in patients with LAH.

The increased prevalence of multiple adenomas and hyperplasia in LAH compared with the overall occurrence in primary HPT

In general, patients with LAH have a higher prevalence of multiglandular disease compared with sporadic HPT (17). Indeed, most cases (85–95%) of sporadic PHP are due to a single adenoma and only 5–10% of the cases are related to multiglandular disease (9). As noted in Table 2, the pathological results published in surgically proven LAH show a higher prevalence of multiglandular disease than expected. This prevalence differs between the various studies, from 18.75 to 83%. Thus, whether or not there is a distinct pathophysiologic process leading to multiglandular rather than single-gland disease, the surgical approach in LAH is controversial. Awad *et al.* (6) consider lithium as an exacerbating factor in patients with a predisposition to develop HPT and are thus best treated with excision of adenomas rather than subtotal parathyroidectomy; Carchman *et al.* (18) support a selective unilateral exploration directed by intraoperative PTH measurement, because in their study the rate of multiglandular disease in patients treated with lithium was not significantly higher (25%) than that in the general population (12.3%). However, Hundley *et al.* (19) claim that follow-up of patients treated by single-gland resection will ultimately show a higher rate of

Figure 2 Mechanism of action of lithium on the calcium-sensing receptor. The calcium sensing receptor is a membranal G-protein-coupled receptor (GPCR). Agonists of the CASR are mainly polyvalent cations. In parathyroid chief cells, the activation of the CASR (black arrow) leads to an interaction between the CASR and the membranal phospholipase C, leading to the production of inositol triphosphate (IP3) and diacylglycerol (DAG). Finally, the elevation of intracellular calcium (Ca-i) seems to activate the phosphorylation of protein-kinase C and inhibits the release of PTH. Paradoxically, lithium, as a monovalent cation, capable to activate GPCR, might be thought to be a weak agonist of the CASR (thin dotted arrow), but rather acts as an inhibitor of the latter, probably by interfering with intracellular molecular pathways. Indeed, lithium inhibits specifically and strongly (transparent thick arrow) the enzyme inositol monophosphatase (IMPase) and reduces the production of IP3 and Ca-i. Thus, lithium might have a dual effect on the CASR; the final effect of lithium on parathyroid chief cells might be the result of a balance between a weak activation at the level of the CASR and a stronger inhibition of intracellular pathways at the level of the IMPase.

recurrence despite the use of intraoperative PTH determination, and that bilateral neck exploration and multigland excisions are the proper way to handle LAH. Abdullah *et al.* (20) express a very similar view and suggest that LAH reflects a spectrum of disease from single to multigland involvement with a variable response of each parathyroid gland to the continuous PTH stimulation. In our cases, the intraoperative decrease of PTH was a good prognostic marker of successful surgery, and led to four-gland exploration when indicated by the laboratory results.

The use of cinacalcet hydrochloride in LAH

Calcimimetics are indicated in the treatment of secondary hyperparathyroidism, but although it appears to be a promising alternative to surgery (21), their role in the treatment of primary HPT remains to be specifically defined. Activation of the calcium-sensing receptor by calcimimetics as cinacalcet reduces PTH secretion and parathyroid gland hyperplasia (21) and could thus specifically antagonize the effects of lithium on the parathyroid glands. One publication reports a modest effect on serum PTH levels but normalization of serum calcium levels in two patients with LAH, who

were treated with lithium for more than 15 years and also had stage 3 chronic kidney disease (22). Another report (23) describes good clinical and laboratory response to cinacalcet (30 up to 120 mg/day) in three patients with lithium-associated hypercalcemia or HPT, who also had impaired renal function but could not discontinue the lithium therapy. In the case we describe, cinacalcet neutralized the effect of lithium on the parathyroid gland with regard to serum calcium levels, with modest but significant effect on PTH levels.

Timing of lithium therapy and its discontinuation with regard to calcium homeostatic disorders

Occurrence of hypercalcemia was described after a treatment period as short as 1 day (24), and a single infusion of lithium in healthy individuals leads to the immediate elevation of serum PTH (25). Overt HPT was described after a period of treatment as short as 1–2 months (26). It seems that there is a cumulative linear increased incidence of LAH correlated to the duration of treatment (7). However, LAH may occur many years after discontinuation of lithium (27, 28). In these cases, a causative relation between the use of lithium and the disease might be confirmed as related before, by the finding on surgery of hyperplastic parathyroid glands as in our first patient, or by the finding of a multiglandular disease as described by Hundley *et al.* (19) in three patients who discontinued lithium 5–14 months before surgery. Some authors claim that lithium may also lead to single PTA (6, 18). However, one cannot definitely rule out a fortuitous association when a single PTA is found years after lithium discontinuation. In patients with LAH, who discontinue lithium therapy, there are some reports of fast resolution of the disease (29, 30) when the duration of treatment was relatively short, up to 5 years; but hypercalcemia may not improve for as long as 8.5 weeks (7), especially after a long duration of lithium therapy (over 5 years of treatment), and will require surgery (18, 19, 29, 31, 32). In these cases, one could also propose the use of cinacalcet instead of surgery as a first-line therapy. Surgery might be reserved as a second-line therapy in cases of resistant LAH or after resurgence of HPT following discontinuation of cinacalcet.

Lithium, calciuria, and bone effect

As discussed earlier, lithium-induced inactivation of the CASR should be characterized by hypocalciuric hypercalcemia. This pattern was described in many patients with LAH, and suggested a reduced rather than increased bone resorption as seen in typical primary HPT (13). However, many cases of LAH are associated with hypercalciuria (or nephrolithiasis), as in two of our patients and also in published case series (6, 17–19) or

case reports. In these cases, an increased bone resorption with low BMD revealing osteoporosis is expected. This finding underscores once again the wide range of laboratory features that can be found in patients with LAH, but in a way it challenges the concept that lithium antagonizes the CASR, and thus warrants further considerations: first, even in patients with typical FHH due to inactivating mutations of the CASR, some cases of hypercalciuria or nephrolithiasis were described (14), and thus, lithium-induced inhibition of the CASR is still possible in such cases. Second, instead of considering isolated levels of urinary calcium, it should be more judicious to evaluate the fractional excretion of calcium, which is usually less than 0.01 in cases of inactivated CASR (patients with FHH) and higher in patients with primary HPT (14). Furthermore, one should check concomitant use of the widely used diuretic *furosemide* which reduces blood levels of calcium but increases urinary levels of calcium. Finally, in our two patients with LAH and hypercalciuria, lithium was stopped years before the finding of hypercalciuria, suggesting that maybe the duration of lithium-related side effects (antagonism of the CASR) are longer in the parathyroid tissues than in the kidneys. However, one cannot totally rule out that hypercalciuria may reveal a previously undiagnosed PTA in a patient treated with lithium. Thus, the issue of why some patients treated with lithium present hypercalciuria, and others do not, remains to be more thoroughly evaluated, including correlation with BMD.

The association of LAH and thyroid carcinoma

In two (50%) of our patients, papillary thyroid carcinoma (PTC) was reported incidentally. McHenry *et al.* (33) also report three cases of associated thyroid carcinoma among a series of eight patients undergoing parathyroidectomy for LAH and Abdullah *et al.* also describe one case of occult PTC among 11 patients with LAH (20). An increased prevalence of up to 2% associated occult thyroid malignancy and PTA in patients undergoing neck surgery for parathyroidectomy (34), and it was suggested that thyroid evaluation before such a surgical procedure is mandatory and simultaneous thyroidectomy should be considered. We could not find enough data to calculate the prevalence of thyroid carcinoma in patients with LAH, but it should probably be considered in the preoperative workup.

Conclusions

In conclusion, LAH is a clinical situation that can alter the success of lithium in treating bipolar disorders. The exact mechanism by which LAH occurs is still uncertain, but it leads, in our view, to both exacerbation of a pre-existing state of HPT as well as to multiglandular disease, probably by leading to an inhibition

of the CASR at the surface of the parathyroid cells. LAH is more frequent in women than men, as in primary HPT. Discontinuation of lithium is frequently impossible, and does not necessarily lead to normalization of calcium levels in all cases. Thus, parathyroidectomy is recommended. The issue of routine four gland exploration and subtotal parathyroidectomy versus intraoperative PTH determination guided excision of simple adenomas or enlarged glands is still unresolved. In the last few years, the development of the calcimimetics might offer a 'medical parathyroidectomy' (21) in patients who are not candidates for surgery.

Declaration of interest

We declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received 5 November 2008

Accepted 8 November 2008