Parathyroidectomy for Tertiary Hyperparathyroidism Associated With X-linked Dominant Hypophosphatemic Rickets

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Background: X-linked dominant hypophosphatemic rickets (XLHR) is a hereditary metabolic bone syndrome that is only beginning to be understood and is rarely associated with progression to irreversible tertiary hyperparathyroidism. We report our surgical experience with 6 patients with XLHR who underwent parathyroidectomy for associated autonomous parathyroid hyperfunction.

Hypothesis: Parathyroidectomy can successfully treat tertiary hyperparathyroidism in the setting of XLHR, although an understanding of expected operative findings and postoperative complications is essential.

Design: The study group comprised 6 patients with XLHR identified from our endocrine surgery database. Presentation, surgical procedure, parathyroid pathologic findings, and subsequent outcome are outlined.

Results: There were 4 women and 2 men. All were exposed to long-term vitamin D and phosphate supplementation therapy. All had persistently elevated preoperative levels of parathyroid hormone and serum calcium. The patients were treated as follows: 3 had total parathyroidectomy, 2 had 3 parathyroid glands identified and resected, and 1 had 2 abnormal parathyroid glands resected with 2 normal-appearing parathyroid glands left in situ. One patient subsequently required completion parathyroidectomy for recurrent disease. Pathologic examination results revealed hyperplasia of all resected parathyroid glands in 4 of 6 patients. One patient had a single adenoma with 3-gland hyperplasia, and 1 patient had a double adenoma. The principal complication of this procedure was profound symptomatic hypocalcemia requiring intravenous calcium infusion. Hungry bone syndrome was also observed in most subjects. Long-term, all patients achieved normocalcemia.

Conclusion: Tertiary hyperparathyroidism is a rare but recognized complication of XLHR. Parathyroidectomy effectively treats this complication caused by autonomous parathyroid hyperfunction, but profound postoperative hypocalcemia necessitates careful management.

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underwent parathyroidectomy for tertiary hyperparathyroidism, emphasizing surgical pathologic characteristics and postoperative care.

METHODS

This retrospective case review details a series of patients with known XLHR who underwent parathyroidectomy for tertiary hyperparathyroidism. The study group comprised 5 patients who underwent surgery at the University of Sydney Endocrine Surgical Unit, Sydney, Australia, and 1 patient who received treatment from 1 of us (S.F.) but who underwent surgery at another hospital. Available medical records were reviewed, and clinical presentation, surgical procedure, parathyroid pathologic features, postoperative care, and subsequent outcome are reported.

RESULTS

There were 4 women and 2 men in the study group. Three were known to have inherited the disease, while the remaining 3 were identified as having sporadic disease. None of the subjects in this study were related. All had clinically and radiologically evident rachitic bone disease, and all had undergone corrective osteotomy during childhood. All were exposed to long-term oral vitamin D and phosphate supplementation—often at doses as high as 8 g of phosphate daily in divided doses. The average length of medical treatment prior to surgical consultation for tertiary hyperparathyroidism was more than 20 years (range, 15-34 years). All had persistent elevations in both their serum calcium and parathyroid hormone (PTH) levels prior to surgical intervention, and 3 had elevations in their serum creatinine levels (Table 1).

The 6 initial operative procedures included 1 2-gland excision, 2 3-gland excisions, and 3 total parathyroidectomies. Four of the patients had a single parathyroid procedure. Two had multiple procedures. One had a completion parathyroidectomy for recurrent hyperparathyroidism, and the other had an incidental final parathyroid gland removed during completion hemithyroidectomy for incidental micropapillary carcinoma. Five patients had multiglandular hyperplasia (1 with an additional adenoma in 1 gland), and 1 patient had 2 adenomas. The average mass of each excised parathyroid gland was 824 mg (range, 70-4400 mg for 18 of the 22 glands with specimen mass documented on pathologic examination).

The average hospital stay in this study was more than 1 week (range, 2-16 days), excluding the hospitalization for a completion thyroidectomy. Symptomatic hypocalcemia was noted postoperatively in 5 of 6 patients, requiring intravenous calcium administration in 4 patients. Two patients required continuous calcium infusion. One of these required infusion for 15 days prior to stabilization of calcium levels and eventual hospital discharge. Strikingly, 4 patients demonstrated postoperative hungry bone syndrome—prolonged and profound postoperative hypophosphatemia and hypocalcemia. Aside from the expected hypocalcemia, the only notable operative complication was a wound infection successfully treated with intravenous antibiotics.

All patients continued taking both oral calcium and vitamin D supplements after they were discharged from the hospital. All patients in this study had eventual postoperative normalization of serum PTH and calcium levels. As noted earlier, 1 patient had recurrence of hyperparathyroidism necessitating completion parathyroidectomy a decade after initial operative intervention. All surviving patients remained normocalcemic while taking oral calcium and vitamin D supplements (Table 2).

COMMENT

Parathyroid function is typically normal in the untreated state of XLHR. Current medical therapy for this hereditary metabolic disease includes high-dose oral phosphate and vitamin D metabolites; it is typically after initiation of high-dose phosphate supplements that initial elevations in serum PTH levels have been noted. Serial depressions in serum calcium levels resulting from high-dose oral phosphate regimens are the proposed cause of the secondary hyperparathyroidism in many patients with XLHR. While this stimulation of the parathyroid glands can typically be quieted by altering the medical regimen, several case reports have documented the evolution to tertiary hyperparathyroidism in this disease process. The calcium infusion test has previously been used to clinically distinguish between cases of secondary and tertiary hyperparathyroidism. In secondary hyperparathyroidism, an infusion of calcium can decrease PTH-mediated renal phosphate loss. Alon et al demonstrated that this tool could also be used in patients with XLHR. In contrast to patients with secondary hyperparathyroidism, those who have progressed to irreversible parathyroid gland hyperfunction show no decrease in PTH-mediated phosphaturia following calcium infusion.

The surgeon typically becomes involved with patients with XLHR following many years of successful medical therapy. Our study reveals that the evolution to autonomous (tertiary) parathyroid hyperfunction may not occur for decades in the few patients with XLHR who will face this complication. The persistent elevations in serum PTH and calcium levels in patients with tertiary hyperparathyroidism necessitate surgical intervention. At this critical juncture, the physician is unable to continue medical treatment, including high doses of vitamin D, in these patients with hypercalcemia. Once tertiary hyperparathyroidism ensues, operative resection is the only effective treatment modality.

OPERATIVE APPROACH

Surgical treatment for such autonomous hyperfunction of the parathyroid glands was first successfully demonstrated by McPhaul in 1964. As seen in most reports in the literature, the tertiary hyperparathyroidism in that case was associated with advanced renal disease. Glandular pathologic examination has most often demonstrated multiple-gland hyperplasia in tertiary hyperparathyroidism, although 1- or 2-gland adenomatous change has been reported in 0% to 30% of patients in various studies. In these instances, removal of only the apparently affected parathyroid glands has been shown to have comparable long-term cure rates. Nonetheless, open par-
athyroidectomy with identification and evaluation of all parathyroid tissue has remained the goal in cases of tertiary hyperparathyroidism.

The surgical treatment for tertiary hyperparathyroidism associated with XLHR has not been firmly established in the literature. In a previous article by Albright and Nussbaum, the term “hungry bone syndrome” was first coined to describe patients who had undergone parathyroidectomy and developed prolonged hypophosphatemia and hypocalcemia, often associated with tetany. More recently, Brasier and Reinfenstein used the term to describe patients who have low levels of serum calcium and phosphorus persisting at least 3 days postoperatively. Using this strict definition, hungry bone syndrome was noted to occur at a rate of 12.6% in their large series of patients following parathyroid resection for primary hyperparathyroidism.

Table 1. Patients With XLHR: Preoperative Presentation and Pertinent Laboratory Values

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age at Surgery, y</th>
<th>Skeletal Involvement</th>
<th>Preoperative Treatment*</th>
<th>Preoperative Laboratory Values†</th>
<th>Years of Medical Therapy Prior to Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/47</td>
<td>Trouble walking at age 4 y; bilateral femoral osteotomies at age 15 y; diagnosis by bone biopsy at age 32 y; sporadic disease</td>
<td>Prescribed vitamin D and phosphate supplements at age 32 y; maximum: 500 000 U of ergocalciferol and 5 g of phosphate per day; ergocalciferol supplements stopped 3 y prior to operation</td>
<td>Serum calcium = 2.69-2.90 mmol/L; PTH = 2.59-2.90 ng/mL; serum creatinine = 0.00013 µmol/L</td>
<td>15</td>
</tr>
<tr>
<td>2/F‡</td>
<td>A. Age 42 Diagnosis at age 18 mo; initial osteotomy at age 8 y; second osteotomy at age 15 y; sporadic disease</td>
<td>Prescribed vitamin D supplements at age 8 y; prescribed phosphate supplements at age 21 y</td>
<td>A. Serum calcium = 3.21-3.29 mmol/L; serum creatinine = 0.00024 µmol/L</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>B. Age 51</td>
<td></td>
<td>B. Serum calcium = 2.65 mmol/L; PTH = 8.37 ng/mL; serum creatinine = 0.00017 µmol/L</td>
<td>17</td>
</tr>
<tr>
<td>3/F/19</td>
<td>Bilateral femoral osteotomy at age 3.5 y; left tibial osteotomy at age 5.5 y; right tibial osteotomy at age 11 y; inherited disease</td>
<td>Prescribed vitamin D and phosphate supplements at age 2 y; supplements stopped because of hypercalcemia</td>
<td>Serum calcium = 2.82-3.29 mmol/L; PTH = 219 ng/mL; serum creatinine = 0.00009 µmol/L</td>
<td>21</td>
</tr>
<tr>
<td>4/F/59</td>
<td>Bilateral femoral osteotomies at age 4 y; bone biopsy at age 43 y leads to initial diagnosis of consistent with crutch walking parathyroid osteopathy; sporadic disease</td>
<td>Prescribed vitamin D supplements at age 38 y; phosphate supplements (up to 8 g/d) added</td>
<td>Serum calcium = 2.95 mmol/L; PTH = 1.09 ng/mL</td>
<td>19</td>
</tr>
<tr>
<td>5/M/50</td>
<td>2 Bilateral femoral osteotomies; spinal stenosis; inherited disease</td>
<td>Diagnosis at age 33 y; prescribed phosphate (4 g/d) and vitamin D supplements</td>
<td>Serum calcium = 2.64-2.79 mmol/L; iPTH = 19.8 pmol/L; serum creatinine = 0.00013 µmol/L</td>
<td>17</td>
</tr>
<tr>
<td>6/M/21</td>
<td>Diagnosis at age 18 mo; short stature, considered for growth hormone; osteotomy at age 16 y; dentition problems; inherited disease</td>
<td>Prescribed phosphate supplements at age 20 mo; prescribed vitamin D supplements at age 2 y; phosphate increased to a maximum of 5 g/d</td>
<td>Serum calcium = 2.65 mmol/L; PTH = 17.5 pmol/L</td>
<td>19</td>
</tr>
</tbody>
</table>

Abbreviations: iPTH, intact parathyroid hormone; PTH, parathyroid hormone; XLHR, X-linked dominant hypophosphatemic rickets.

SI conversions: To convert serum calcium levels from millimoles per liter to milligrams per deciliter, divide by 0.25; serum creatinine levels from micromoles per liter to milligrams per deciliter, divide by 88.4.

*Vitamin D supplements were oral vitamin D metabolites.
†Normal range for serum calcium level is 2.05 to 2.55 mmol/L; PTH level for patients 1 and 4, lower than 0.04 ng/mL; PTH level for patients 2 and 3, 12 to 72 ng/mL; PTH level for patient 6, 1 to 7 pmol/L; iPTH level, 1.1 to 6.9 pmol/L; and serum creatinine level, 0.00005 to 0.00008 µmol/L. Ranges for PTH levels reflect the evolving assays used across several decades in Australia.
‡A refers to the patient’s first surgery; B, the patient’s second surgery.

POSTOPERATIVE CARE

The complication of hypocalcemia following extensive parathyroidectomy has been well documented in patients with tertiary hyperparathyroidism. We found no previous discussion in the literature, which details the particular challenge of postoperatively managing patients with XLHR who have undergone parathyroidectomy. The hospital course in such patients is rarely uneventful, as our experience with often profound periods of metabolic instability highlights.

The term hungry bones was first coined by Albright and Reinfenstein in 1948 to describe a subset of patients who had undergone parathyroidectomy and developed prolonged hypophosphatemia and hypocalcemia, often associated with tetany. More recently, Brasier and Nussbaum used the term to describe patients who have low levels of serum calcium and phosphorus persisting at least 3 days postoperatively. Using this strict definition, hungry bone syndrome was noted to occur at a rate of 12.6% in their large series of patients following parathyroid resection for primary hyperparathyroidism.
### Table 2. Patients With XLHR: Operative Findings and Postoperative Course

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Parathyroid Procedure, Operative Findings</th>
<th>Pathologic Examination Results</th>
<th>Postoperative Laboratory Values and Hospital Course*</th>
<th>Subsequent Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-Gland excision</td>
<td>Chief cell adenomas in 2 glands; RS = 1.8 × 1.2 × 1.0 cm; RI = 2.3 × 1.0 × 1.0 cm</td>
<td>Serum calcium = 1.85 mmol/L with parathyroid tissue (ie, RI gland); PTH level = 0.3-0.7 mmol/L on POD 5; diagnosis of HBS; discharged POD 6</td>
<td>Serum calcium = 2.47 mmol/L and PTH = 0.31 ng/mL; both normalized; patient died of intracranial hemorrhage 8 mo postoperatively</td>
</tr>
<tr>
<td>2†</td>
<td>A. 3-Gland excision and right hemithyroidectomy; An apparent large RS gland excised; right hemithyroid with apparent RI gland attached; enlarged LS gland removed; Li gland not identified</td>
<td>A. RS = 2g, 2.7 × 1.7 × 1.0 cm, hyperplastic; right hemithyroid = MNG with parathyroid tissue (ie, RI gland); LS = 1.5 × 0.9 × 0.5 cm, hyperplastic gland</td>
<td>A. Serum calcium = 2.44 mmol/L; patient’s postoperative serum calcium level stable; discharged POD 2; B. Postoperative 15-min PTH dropped to a normal level (37.9 ng/mL); symptomatic hypocalcemia treated with 3 doses of IV calcium on PODs 1, 2, and 3; serum calcium = 2.01 mmol/L; phosphorus = 0.98 mmol/L on POD 5; diagnosis of HBS; discharged POD 6</td>
<td>A. Stable serum calcium level for 6 y; subsequent recurrence of hypercalcemia (serum calcium level = 3.1 mmol/L, preoperatively) for 18 mo prior to second operation; B. Remained normocalcemic (serum calcium level = 2.48 mmol/L); PTH level = 21 ng/mL; serum creatinine level has remained elevated (0.00024 µmol/L)</td>
</tr>
<tr>
<td>3</td>
<td>Total parathyroidectomy with 30-mg SCM autotransplant</td>
<td>RS = 4.4 g adenoma; remaining 3 glands are hyperplastic (1.0, 0.11, and 0.1 g)</td>
<td>Significant postoperative symptomatic hypocalcemia (serum calcium = 1.85 mmol/L requiring continuous IV infusion for 1 to POD 15)</td>
<td>Serum calcium level (2.34 mmol/L and PTH level (28.5 ng/mL) both normalized and remain in normal range</td>
</tr>
<tr>
<td>4</td>
<td>Total parathyroidectomy, thyroidectomy, and cervical thymectomy</td>
<td>4-Gland hyperplasia; RS = 0.23 g, LS = 0.69 g, RI = 0.1 g, Li = 0.07 g</td>
<td>Symptomatic hypocalcemia only requiring increase in ergocalciferol to 1 µg/d; minimal paresthesias and tetany resolved after 2 wk postoperatively</td>
<td>Serum calcium level (2.17 mmol/L) normalized</td>
</tr>
<tr>
<td>5</td>
<td>Total parathyroidectomy, left hemithyroidectomy</td>
<td>5-Gland hyperplasia, all glands = 0.1 g; papillary carcinoma of thyroid in removed left hemithyroid; residual thymic tissue benign on completion thyroidectomy with embedded 6th hyperplastic parathyroid gland present; size undocumented</td>
<td>No symptomatic hypocalcemia; sestamibi scan on POD 5 showed no evidence of residual parathyroid tissue; wound infection treated with IV cephalixin for 6 d; discharged POD 6</td>
<td>Serum calcium (2.42 mmol/L and PTH (1.6 pmol/L) levels normalized and remain normal</td>
</tr>
<tr>
<td>6</td>
<td>3-Gland parathyroidectomy and cervical thymectomy; A very large Li gland and both superior glands (slightly enlarged) removed; a biopsy was performed on apparently normal RI gland (possible fourth gland)</td>
<td>Li = 2.97 g, hyperplasia; LS = 0.46 g; RS = 0.41 g, hyperplasia; biopsy results demonstrate normal thymic tissue without evidence of parathyroid tissue</td>
<td>Profound symptomatic hypocalcemia (serum calcium = 1.68 mmol/L with muscle spasm requiring continuous IV calcium infusion across 4 d; phosphorus = 1.99 mmol/L on POD 7; diagnosis of HBS; discharged POD 9</td>
<td>Serum calcium level normalized 1 wk postoperatively (2.2 mmol/L) and PTH = 1.4 pmol/L; calcium and PTH levels remain normal</td>
</tr>
</tbody>
</table>

Abbreviations: HBS, hungry bone syndrome; iPTH, intact parathyroid hormone; IV, intravenous; Li, left inferior gland; LS, left superior gland; MNG, multinodular goiter; POD, postoperative day; PTH, parathyroid hormone; RI, right inferior gland; RS, right superior gland; SCM, sternocleidomastoid; XLHR, X-linked dominant hypophosphatemic rickets.

SI conversions: To convert serum calcium levels from millimoles per liter to milligrams per deciliter, divide by 0.25; serum creatinine levels from micromoles per liter to milligrams per deciliter, divide by 88.4; phosphorus from micromoles per liter to milligrams per deciliter, divide by 0.323.

*Normal range for serum calcium level is 2.05 to 2.55 mmol/L; serum creatinine level, 0.00005 to 0.00008 µmol/L; phosphorus level for patients 1, 2, and 3, 0.8 to 1.55 mmol/L; phosphorus level for patient 6, 2.20 to 2.55 mmol/L; PTH level for patient 1, lower than 4 ng/mL; PTH level for patients 2 and 3, 12 to 72 ng/mL; iPTH level, 0.6 to 4.2 µmol/L. Ranges for phosphorus and PTH levels reflect the evolving assays used across several decades in Australia.

†A refers to the patient’s first surgery; B, to the patient’s second surgery.

Our study suggests a much higher incidence of hungry bone syndrome following parathyroidectomy in patients with XLHR. The combination of chronic phosphate depletion and postoperative hypocalcemia might be expected to predict a period of marked mineral depletion in many of these patients. In addition to the under-
lying metabolic derangements, parathyroid gland size may also explain the increased incidence of hungry bone syndrome. The average mass of each excised parathyroid gland in our study was 824 mg (normal parathyroid gland size, <70 mg), which may reflect the duration and intensity of parathyroid stimulation in this subset of patients with tertiary hyperparathyroidism. Size of the resected parathyroid tissue is the strongest predictor of hungry bone syndrome following parathyroidectomy. Of course, the metabolic complications of this disorder are more than just the result of tertiary hyperparathyroidism. It may also be that the hungry bone syndrome in these patients may actually be a manifestation of hyperparathyroidism in patients who already (and still) have an inability to reabsorb phosphate. It is, in fact, possible that parathyroidectomy, by removing PTH, may aggravate the primary abnormality in this syndrome.

Our study suggests that the management of patients with XLHR following parathyroidectomy is intrinsically complicated. This expectation may lead the surgeon to consider an increased preoperative loading dose of vitamin D to stimulate intestinal absorption of calcium and phosphate, thus attenuating the metabolic shifts following surgery. Intraoperatively, a prophylactic calcium infusion might also be considered in the patient at high risk for profound postoperative hypocalcemia. Postoperatively, it has been suggested that serum calcium levels be monitored as frequently as every 4 hours in patients likely to develop hungry bone syndrome.24

Tertiary hyperparathyroidism is a rare complication that develops in a subset of patients with XLHR. It is typically noted after many years of treatment with high-dose oral phosphate and vitamin D supplements—the accepted medical regimen for this hereditary metabolic bone disease. Once tertiary hyperparathyroidism ensues, medical therapy cannot be continued in the face of hypercalcemia. As the only effective intervention available, parathyroidectomy can effectively cure this autonomous parathyroid hyperfunction, as our series demonstrates. The surgeon should surgically explore all parathyroid tissue because multiglandular involvement is to be expected. The underlying phosphate wasting inherent in these patients, combined with hypocalcemia following extensive parathyroid surgery, is associated with a very high incidence of hungry bone syndrome in our series. An understanding and expectation of such will aid the surgeon in managing the often complicated postoperative course for patients with XLHR following parathyroidectomy.

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CONCLUSIONS

Tertiary hyperparathyroidism is a rare complication that develops in a subset of patients with XLHR. It is typically noted after many years of treatment with high-dose oral phosphate and vitamin D supplements—the accepted medical regimen for this hereditary metabolic bone disease. Once tertiary hyperparathyroidism ensues, medical therapy cannot be continued in the face of hypercalcemia. As the only effective intervention available, parathyroidectomy can effectively cure this autonomous parathyroid hyperfunction, as our series demonstrates. The surgeon should surgically explore all parathyroid tissue because multiglandular involvement is to be expected. The underlying phosphate wasting inherent in these patients, combined with hypocalcemia following extensive parathyroid surgery, is associated with a very high incidence of hungry bone syndrome in our series. An understanding and expectation of such will aid the surgeon in managing the often complicated postoperative course for patients with XLHR following parathyroidectomy.

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REFERENCES