A case of severe hungry bone syndrome following parathyroidectomy analyzed with a focus on the alpha-Klotho calcium regulator

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Abstract

Introduction
Hungry bone syndrome is a complication following parathyroid surgery where the correction of primary hyperparathyroidism is associated with unregulated bone mineralization, inducing severe and prolonged hypocalcaemia. The mechanisms for hungry bone syndrome are neither clear nor has a method for its prevention been established.

Case
The patient was a 29-year-old woman. She had problems with her gait due to femur pain. The serum calcium, parathyroid hormone and alkaline phosphatase levels were elevated. Preoperative imaging indicated a parathyroid tumour posterior to the right thyroid lobe. She was diagnosed with primary hyperparathyroidism and underwent parathyroidectomy. Despite bisphosphonates and intensive calcium and vitamin D supplementation, the serum level of calcium remained low due to hungry bone syndrome.

Discussion
We analyzed hungry bone syndrome focusing on the discrepancy between hypocalcaemia and low-level parathyroid hormone in terms of the alpha-Klotho calcium regulator.

Case report
A 29-year-old woman presented to our hospital with eight-month coxalgia in November 2011. In addition, she had gait disturbance due to femur pain. The pelvic X-ray showed a lytic lesion of the right acetabular roof because of severe osteoporosis.

Figure 1: The pelvic X-ray shows a lytic lesion of the right acetabular roof because of severe osteoporosis.

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surgery, a single large parathyroid tumour was removed. No other parathyroid lesions were detected. The tumour was pathologically determined to be parathyroid adenoma. Two days following the operation, the patient complained of tetany and the preoperative serum calcium level of 13.3 mg/dL was reduced promptly to 7.7 mg/dL. Despite intravenous and oral calcium supplementation and vitamin D supplementation, the serum level of calcium remained low due to HBS after the operation. Irrespective of the persistent hypocalcaemia, the serum intact PTH level could not be elevated. Urinary calcium excretion was consistently <0.5 g/day. The serum alkaline phosphatase (ALP) activity of skeletal isozyme temporarily increased to >3500 IU/L. The patient was discharged 14 days after her operation since she did not show any particular symptoms. A laboratory study performed 14 days after the operation showed a serum calcium level of 7.6 mg/dL and a phosphorous level of 2.8 mg/dL. This was only because of oral calcium and vitamin D normalized to age-, sex- and ethnicity-matched controls, was 68% and −2.9 SD preoperatively.

The patient received bisphosphonate for hypercalcaemia (first zoledronate 4 mg/day for two days, followed by oral alendronate 15 mg/day) and elicitonin (40 unit/day) treatment until the operation. The serum calcium level of 15 mg/dL decreased to 13.3 mg/dL. Then she underwent parathyroidectomy. At

**Table 1 Laboratory data**

<table>
<thead>
<tr>
<th>Haematological studies</th>
<th>Endocrinological studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucocyte 6700/mm³</td>
<td>Intact parathyroid hormone 1860 pg/mL</td>
</tr>
<tr>
<td>Erythrocyte 432 x 10⁶/mm³</td>
<td>Calcitonin 28 pg/mL</td>
</tr>
<tr>
<td>Haemoglobin 12.6 g/dL</td>
<td>Free T4 0.6 ng/dL</td>
</tr>
<tr>
<td>Platelet 24.1 x 10⁹/mm³</td>
<td>Free T3 3.3 pg/mL</td>
</tr>
<tr>
<td>Blood chemistry</td>
<td>Thyroid-stimulating hormone 3.7 μU/mL</td>
</tr>
<tr>
<td>Albumin 4.3 g/dL</td>
<td>Luteinizing hormone 6.7 mU/mL</td>
</tr>
<tr>
<td>Alkaline phosphatase 4762 IU/L</td>
<td>Follicle stimulating hormone 4.9 mU/mL</td>
</tr>
<tr>
<td>Fasting blood glucose 88 mg/dL</td>
<td>Growth hormone 2.1 ng/mL</td>
</tr>
<tr>
<td>Calcium 15 mg/dL</td>
<td>Prolactin 22.5 ng/mL</td>
</tr>
<tr>
<td>Inorganic phosphate 2.5 mg/dL</td>
<td>Adrenocorticotropic hormone 15.9 pg/mL</td>
</tr>
<tr>
<td>1,25-(OH)₂ Vit. D 103 pg/mL</td>
<td>Immunoreactive insulin 4.6 μU/mL</td>
</tr>
<tr>
<td>HbA₁c 4.6%</td>
<td>C-peptide reactivity 0.8 ng/mL</td>
</tr>
<tr>
<td>Urinary excretion</td>
<td>Gastrin 37 pg/mL</td>
</tr>
<tr>
<td>Calcium 9.7 mg/dL</td>
<td>NTx/creatinine 784.5 nmol BCE/mmol Cr</td>
</tr>
<tr>
<td>Phosphate 43.4 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>
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Figure 3: Computed tomography of the neck. A well-enhanced mass was inferior to the right lobe with no invasion to the neighbouring organs.

Figure 4: MIBI scan. Left: 20-minute delayed image. Right: 2-hour delayed image. These images of technetium-99m-MIBI are consistent with right-sided parathyroid adenoma.

That the preoperative calcium concentration was not related to the occurrence of hypocalcaemia\(^2,6\). Some researchers recommend the administration of bisphosphonate to prevent HBS in patients with PHPT\(^2,7\). Bisphosphonate has a potent effect on the inhibition of osteoclastic bone resorption and is widely used in the treatment of osteoporosis and hyperparathyroidism\(^8-10\). In the present case, despite bisphosphonate supplementation before the operation and intensive calcium and vitamin D supplementation after the operation, the serum level of calcium remained low. Currently, the methods for preventing HBS remain controversial.

Recently, a new calcium homeostasis regulator was discovered and named \(\alpha\)-Klotho\(^3,11\). \(\alpha\)-Klotho is a unique molecule that plays pivotal roles in the rapid tuning of the extracellular Ca\(^{2+}\) concentration through transepithelial Ca\(^{2+}\) transport and PTH secretion. This results in a subsequent Ca\(^{2+}\) increase in the serum. Through these pathways, \(\alpha\)-Klotho participates in the regulation of calcium homeostasis of the cerebrospinal fluid (CSF) and blood/body fluids by its actions in the choroid plexus, parathyroid glands and distal convoluted tubule (DCT) nephrons. In this respect, \(\alpha\)-Klotho is a key player that integrates a multi-step regulatory system of calcium homeostasis that rapidly adjusts the extracellular calcium concentration and continuously maintains its concentration within a narrow physiological range\(^11\).

We focused the discrepancy between hypocalcaemia and the low-level of PTH in the present case of HBS. According to the central theory of serum Ca concentration, hypocalcaemia stimulates the secretion of PTH and the serum calcium level is rapidly elevated. However, in our patients, the serum PTH level remained low two weeks following the operation despite hypocalcaemia. With respect to this incomprehensible problem, we referred to Björklund’s report, which noted that \(\alpha\)-Klotho mRNA supplementation. After five months, her serum level of calcium and ALP became normalized.

Discussion

HBS is a postoperative complication of PHPT due to unregulated bone mineralization. It results in severe and prolonged hypocalcaemia. Braiser and Nussbaum followed 198 patients after operation for PHPT. They found that the risk factors for the development of HBS included high preoperative levels of serum calcium, PTH, ALP, blood urea nitrogen (BUN), large parathyroid adenoma and old age\(^1\). Our patient’s laboratory findings included high levels of intact PTH, serum calcium and ALP. In addition, the patient had a large parathyroid adenoma and severe osteoporosis. She was categorized as a high-risk patient for HBS.

The prevention of HBS has not yet been established. Smith et al have recommended that preoperative treatment with calcitriol for 5–10 days may prevent HBS in the post-parathyroidectomy state\(^4,5\). However, Mittendorf et al and I-Te Lee et al have reported

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A significant risk factor of HBS may be not the high calcium concentration, but the duration of the normalized calcium concentration. Accordingly, α-Kl can be restored and can secrete PTH whenever calcium is decreased. Serum soluble α-Kl can be measured by the ELISA method. Therefore, measurement of serum soluble α-Kl may predict potential cases of HBS immediately after parathyroidectomy.

Further examinations for HBS and α-Kl are required in the future. Thus, it is imperative to carefully check for serum calcium and symptoms following an operation. This is especially important when treating high-risk HBS patients.

### Abbreviations list

ALP, alkaline phosphatase; α-Kl, alpha-Klotho; BUN, blood urea nitrogen; CSF, cerebrospinal fluid; CT, computed tomography; DCT, distal convoluted tubule; HBS, hungry bone syndrome; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone.

### Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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### References


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