



A Rare Cause of Hypercalcemia: “Immobilization”. A Case Report and Literature Review

Gulsah Elbuken¹, Bahadır Yazıcıoğlu², Onur Öztürk², Mehmet Derya Demirag³

¹ Department of Endocrinology and Metabolism, Samsun Training and Research Hospital

² Department of Family Medicine, Samsun Training and Research Hospital

³ Chief of Internal Medicine Department, Samsun Training and Research Hospital

Abstract

Immobilization hypercalcemia (IH) mainly results from rapid bone turnover and may be seen after spinal cord injury or long bone fracture in particular in children and adolescents. The pathophysiology of this entity is entirely unknown. A-19 year-old, male quadriplegic adolescent was referred to our outpatient clinic by a family physician. At presentation he had some vague symptoms due to hypercalcemia including fatigue, nausea, vomiting, anorexia, constipation and dehydration. Laboratory investigations for hypercalcemia revealed low intact parathyroid hormone level, low 25-OH vitamin D, and high 24-hour urine calcium. He was diagnosed as having IH after all other causes of hypercalcemia were excluded. The pathophysiology of IH remains unclear. Treatment is directed towards lowering the serum calcium level. Up to date, intravenous hydration with isotonic saline, furosemide and salmon calcitonin have been the conventional therapies. Other treatment options include bisphosphonates (such as etidronate, zoledronate or pamidronate) or, an inhibitor of receptor activator of nuclear factor kappa-B ligand (RANKL), denosumab. IH is a rare cause of hypercalcemia. Physicians should be aware of this condition when seeing patients with restricted physical activity.

Key Words: Hypercalcemia, immobilization, quadriplegia

(Rec.Date: Oct 15, 2014

Accept Date: Jan 16, 2015)

Corresponding Author: Gulsah Elbuken, Samsun Training and Research Hospital, Department of Endocrinology and Metabolism, 55090, Ilkadim, Samsun, Turkey

E-mail: gelbuken@yahoo.com.tr **Phone:** +90 362 277 85 98 **Fax:** +90 362 277 88 65

Introduction

Immobilization hypercalcemia (IH) was first described in 1941 by Albright in a teenager with fracture [1]. IH may be seen after orthopedic fractures, spinal cord injury, Guillain-Barré syndrome, polio and in astronauts after exposure to microgravity in space [2-5]. The increased incidence in older children and adolescents is related to the rapid bone turnover that accompanies growth, whereas that in males is possibly because of their greater bone mass compared to females [3,6]. This disorder is more common in patients with quadriplegia than it is in persons with paraplegia [7]. In the elderly population, IH is usually a sequela of cerebrovascular accident [8].

The mechanism of IH is not yet fully understood. It is believed that muscle activity transmits a bone formation signal through the osteocyte. With immobilization, the mechanical stimulation for bone formation caused by muscle activity is reduced (mechanostat theory), leaving resorption unopposed [9]. Another scenario for IH is the acidic environment created by low blood flow that may impair mineralization of bone [10]. IH stimulates osteoclastic bone resorption. This process causes calcium loss from the bones and hypercalciuria. Hypercalcemia develops when the efflux of calcium from bone exceeds the capacity of the kidney to excrete calcium. Immobilized patients with preexisting states of high bone turnover (in particular, adolescents and patients with Paget's disease, thyrotoxicosis or primary hyperparathyroidism), and/or reduced renal function are at the risk of developing severe hypercalcemia [3,11,12]. Patients with IH have increased rates of bone resorption as shown by elevated urinary hydroxyproline/creatinine ratios (>0.033) and elevated calcium/creatinine ratios (>0.50) [13].

For the diagnosis of immobilization-related hypercalcemia, all the other causes of PTH- and vitamin D-dependent hypercalcemia should be carefully excluded [14]. The therapeutic goals of IH are retardation of bone resorption and enhancement of renal calcium excretion. A passive mobility or weight-bearing rehabilitative program is undoubtedly the curative treatment and should be instituted early. Control of the underlying illness generating immobilization is crucial to foster recovery or alleviation of immobilization. Definitive treatment consists of mobilizing the patient.

Case Report

A 19 year-old male adolescent was referred to our outpatient clinic by a family physician due to hypercalcemia detected in his biochemical tests. The patient was quadriplegic caused by spinal trauma after diving into shallow water. He had been bedridden for 3 years. At presentation, the patient had some vague symptoms due to hypercalcemia such as fatigue, nausea, vomiting, anorexia, constipation and dehydration. His physical examination showed a decubitus ulcer 3x4 cm in size in the sacral region. Laboratory workup revealed hypochromic, microcytic anemia. Additionally, serum calcium was found to be elevated whereas intact parathyroid hormone and 25-OH vitamin D levels were lower than normal levels. 24-hour urine calcium was also elevated. Thyroid and adrenal function tests were in normal limits (Table 1). Abdominal ultrasonographic examination did not show nephrolithiasis. The patient was hospitalized for the treatment of hypercalcemia.

Mobilization of the patient was not possible; thus, the patient was treated with several liters of normal saline each day to expand intracellular volume and to obtain immediate increase in renal clearance of calcium. The urine was acidificated. High fluid and low calcium intake were also recommended. A passive exercise programme was started for the patient. His serum calcium levels were monitored and gradual decline was observed daily. On the seventh day of hospitalization, serum calcium level decreased to 9.9 mg/dL. During his stay, the patient was also followed by plastic surgery specialists and ulcer care was performed daily. His oral food intake was supported by enteral feeding solutions and iron replacement drugs were also added to the diet. Mobilization of the patient is the primary therapy for IH, but mobilization was not possible for our patient. So, the patient was discharged after normalisation of serum calcium levels and referred to another hospital to participate in a physical therapy programme for rehabilitation of quadriplegia.

Six weeks after his discharge, his calcium level remained within normal range. The patient, his family, and also his family physician were advised to check serum calcium level monthly.

Table 1: Biochemical parameters of the patient, before and after the treatment.

Parameter	Pre-treatment	Post-treatment	Reference ranges	Unit
BUN	15	9.7	10-50	mg/dL
Creatinine	0.4	0.5	0.5-1.0	mg/dL
Calcium	13	9.7	8.6-10.2	mg/dL
Phosphate	3	3.9	3.5-4.5	mg/dL
Albumin	3.8	4	3.5-5.2	g/dL
ALP	76		<300	U/L
PTH	5.7		20-75	pg/mL
25-OH vit D	15		30-100	nmol/L
TSH	2.9		0.25-5.00	μIU/mL
ft4	1.32		0.88-1.72	ng/dL
Serum cortisol	12		7-29	μg/dL
Hb	9.6	12.0	13.2-17.2	g/dL
Hct	27.0	35.8	36-45	%
Leukocyte	6920	7400	3500-10000	/mm ³
Thrombocyte	315000	275000	148000-339000	/mm ³
MCV	84	81	85.6-100.0	fL
Ferritin	6		7-276.8	ng/mL
Vitamin B12	230		214-914	pg/mL
Pholate	10		5.38-24	ng/mL
Urine calcium /24-hours	460		100-300	mg/day

BUN: Blood urea nitrogen, ALP: Alkaline phosphatase, PTH: Parathormone, Hb: Hemoglobin, 25-OH vit D: 25 hydroxy-vitamin D3, TSH: Thyroid stimulan hormone, ft4: Thyroxin, MCV: Mean corpucular volume.

Discussion

IH is more common in children and adolescents due to increased rate of bone turnover and it usually develops 4–6 weeks after trauma but it can begin as early as 2 weeks and as late as six months [11].

In the presented case, we have hydrated the patient with intravenous (IV) normal saline. Saline expands the extracellular fluid volume, increases the glomerular filtration rate, and increases the excretion of calcium in the urine. If intravenous saline (with or without furosemide) fails to control hypercalcemia, a second line of medications is usually is needed [15-17]. When the hypercalcemia is severe, initial administration of calcitonin can be used.

Administration of calcitonin effectively decreases the serum calcium concentration but its effect is known to be limited to a few days only because of development of tachyphylaxis [18]. At present, calcitonin is not available in our country. As shown by our case, saline administration alone can control hypercalcemia in some patients, but it needs to be used for the duration of the increased mobilization from bone. In our patient hypercalcemia was improved by saline infusion, but we planned to monitor serum calcium levels periodically. If isotonic saline infusion was not sufficient to decrease serum calcium concentrations we would need to use other treatment choices such as bisphosphonates [4,11].

Pamidronate disodium is a bisphosphonate which acts by inhibiting osteoclast-mediated resorption and by reducing osteoclast viability and it is approved for the treatment of hypercalcemia of malignancy. The drug is administered as a single intravenous (IV) dose and rapidly lowers serum calcium within 3 days [13,19]. Zoledronic acid is another bisphosphonate approved for the treatment of hypercalcemia of malignancy. In randomized clinical trials, zoledronic acid was more effective than pamidronate in lowering serum calcium levels, with a longer duration of action [20]. Aledronate, ibandronate and etidronate are other bisphosphonates that can be used for the treatment of IH which act by inhibiting bone resorption [4,8,15,21].

Gallium and plicamycin have been used to treat hypercalcemia of malignancy, but these compounds have not been used in IH [21,22].

The receptor activator of nuclear factor kappa-B ligand (RANKL) is a protein that acts as the primary signal for bone removal. In many bone loss conditions, RANKL overwhelms the body's natural defenses against bone destruction. Denosumab is designed to inhibit RANKL [23]. Unlike bisphosphonates, denosumab is not contraindicated in patients with renal insufficiency, and the effect is much more prolonged than that of calcitonin. However, clinicians should be aware that considerable hypocalcemia may develop rapidly after administration of denosumab, and perhaps the initial dose of denosumab should be lower than the dose used for other indications [24].

Conclusion

IH commonly occurs in both children and adolescents. IH should be kept in mind as a differential diagnosis for immobile patients with hypercalcemia. If untreated, patients may develop dehydration, personality changes, calcium oxalate nephrolithiasis, and renal failure. Early diagnosis and prompt correction of IH results in avoidance of unnecessary investigations, unwanted recurrences and potentially life-threatening complications.

References

1. Albright F, Burnett CH, Cope O, Parsons W. Acute atrophy of bone (osteoporosis) simulating hyperparathyroidism. *J Clin Endocrinol*. 1941;1:711-716.
2. Tori JA, Hill LL. Hypercalcemia in children with spinal cord injury. *Arch Phys Med Rehabil*. 1978;59(10):443-6.
3. Maynard FM. Immobilization hypercalcemia following spinal cord injury. *Arch Phys Med Rehabil*. 1986;67(1):41-4.
4. Meythaler JM, Korkor AB, Nanda T, Kumar NA, Fallon M. Immobilization hypercalcemia associated with Landry-Guillain-Barré syndrome. Successful therapy with combined calcitonin and etidronate. *Arch Intern Med*. 1986;146(8):1567-71.
5. Stewart AF, Adler M, Byers CM, Segre GV, Broadus AE. Calcium homeostasis in immobilization: an example of resorptive hypercalciuria. *N Engl J Med*. 1982;306(19):1136-40.
6. Benjamin RW, Moats-Staats BM, Calikoglu's A, Savendahl L, Chrysis D. Hypercalcemia in children. *Pediatr Endocrinol Rev*. 2008;5(3):778-84.
7. Naftchi NE, Viau AT, Sell GH, Lowman EW. Mineral metabolism in spinal cord injury. *Arch Phys Med Rehabil*. 1980;61(3):139-42.
8. Sato Y, Asoh T, Kaji M, Oizumi K. Beneficial effect of intermittent cyclical etidronate therapy in hemiplegic patients following an acute stroke. *J Bone Miner Res*. 2000;15(12):2487-94.
9. Bikle DD, Halloran BP. The response of bone to unloading. *J Bone Miner Metab*. 1999;17(4):233-44.
10. Krieger NS, Sessler NE, Bushinsky DA. Acidosis inhibits osteoblastic and stimulates osteoclastic activity in vitro. *Am J Physiol*. 1992; 262(3 Pt 2):F442-8.
11. Massagli TL, Cardenas DD. Immobilization hypercalcemia treatment with pamidronate disodium after spinal cord injury. *Arch Phys Med Rehabil*. 1999;80(9):998-1000.
12. Gopal H, Sklar AH, Sherrard DJ. Symptomatic hypercalcemia of immobilization in a patient with end-stage renal disease. *Am J Kidney Dis*. 2000;35(5):969-72.
13. Gallacher SJ, Ralston SH, Dryburgh FJ, Logue FC, Allam BF, Boyce BF, Boyle IT. Immobilization-related hypercalcaemia--a possible novel mechanism and response to pamidronate. *Postgrad Med J*. 1990;66(781):918-22.

14. Khairallah W, Fawaz A, Brown EM, El-Hajj Fuleihan G. Hypercalcemia and diabetes insipidus in a patient previously treated with lithium. *Nat Clin Pract Nephrol.* 2007;3(7):397-404.
15. Gilchrist NL, Frampton CM, Acland RH, Nicholls MG, March RL, Maguire P, Heard A, Reilly P, Marshall K. Alendronate prevents bone loss in patients with acute spinal cord injury: a randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab.* 2007;92(4):1385-90.
16. Valverde P. Pharmacotherapies to manage bone loss-associated diseases: a quest for the perfect benefit-to-risk ratio. *Curr Med Chem.* 2008;15(3):284-304.
17. Maier JD, Levine SN. Hypercalcemia in the Intensive Care Unit: A Review of Pathophysiology, Diagnosis, and Modern Therapy. *J Intensive Care Med.* 2013 Oct 15. [Epub ahead of print].
18. Ahmad S, Kuraganti G, Steenkamp D. Hypercalcemic Crisis: A Clinical Review. *Am J Med.* 2014 Oct 17. pii: S0002-9343(14)00915-2. [Epub ahead of print].
19. Machado CE, Flombaum CD. Safety of pamidronate in patients with renal failure and hypercalcemia. *Clin Nephrol.* 1996;45(3):175-9.
20. Major P, Lortholary A, Hon J, Abdi E, Mills G, Menssen HD, Yunus F, Bell R, Body J, Quebe-Fehling E, Seaman J. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol.* 2001;19(2):558-67.
21. Pecherstorfer M, Brenner K, Zojer N. Current management strategies for hypercalcemia. *Treat Endocrinol.* 2003;2(4):273-92.
22. Leyland-Jones B. Treating cancer-related hypercalcemia with gallium nitrate. *J Support Oncol.* 2004;2(6):509-16.
23. Yasuda H. RANKL, a necessary chance for clinical application to osteoporosis and cancer-related bone diseases. *World J Orthop.* 2013;4(4):207-17.
24. Booth KA, Hays CI. Using denosumab to treat immobilization hypercalcemia in a post-acute care patient. *J Clin Endocrinol Metab.* 2014;99(10):3531-5.