

# Diagnosis, Management, and Possible Prevention of Hungry Bone Syndrome in an Adolescent with Primary Hyperparathyroidism and Vitamin D Deficiency

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**P** rimary hyperparathyroidism (PHPT) is a rare disorder in children with an incidence estimated at only 2 to 5 cases in 100,000 person-years [1]. The etiology for most cases of childhood and adolescent PHPT is a single parathyroid adenoma. Almost all cases are benign with carcinoma occurring in less than 1% [1].

Pharmacological therapy for hypercalcemia induced by PHPT includes: hydration with 0.9% NaCl solution and pharmacological therapy with loop diuretics (i.e., furosemide), calcitonin, glucocorticoids, and bisphosphonates. Most pediatric patients require parathyroidectomy, which is curative in the majority of cases. Patients with multiple adenomas require more than one operation for a complete cure. Intraoperative measurements of parathyroid hormone (PTH) levels after resecting the adenoma can confirm successful parathyroidectomy. Complications of the surgery include bleeding, damage to the recurrent laryngeal nerve, hypercalcemia (3%), and hypocalcemia due to hungry bone syndrome [1].

Hungry bone syndrome is a well-known complication of parathyroidectomy, especially when high PTH is associated with high bone turnover, such as with vitamin D deficiency. There are scarce data on hungry

bone syndrome and its management in the pediatric population. We report an instructive case of combined primary hyperparathyroidism and vitamin D deficiency and discuss possible treatments for prevention of hungry bone syndrome in this situation.

## PATIENT DESCRIPTION

A previously healthy 15-year-old girl presented to the endocrine clinic with right leg pain and limping without a history of trauma. The following tests and examinations were performed:

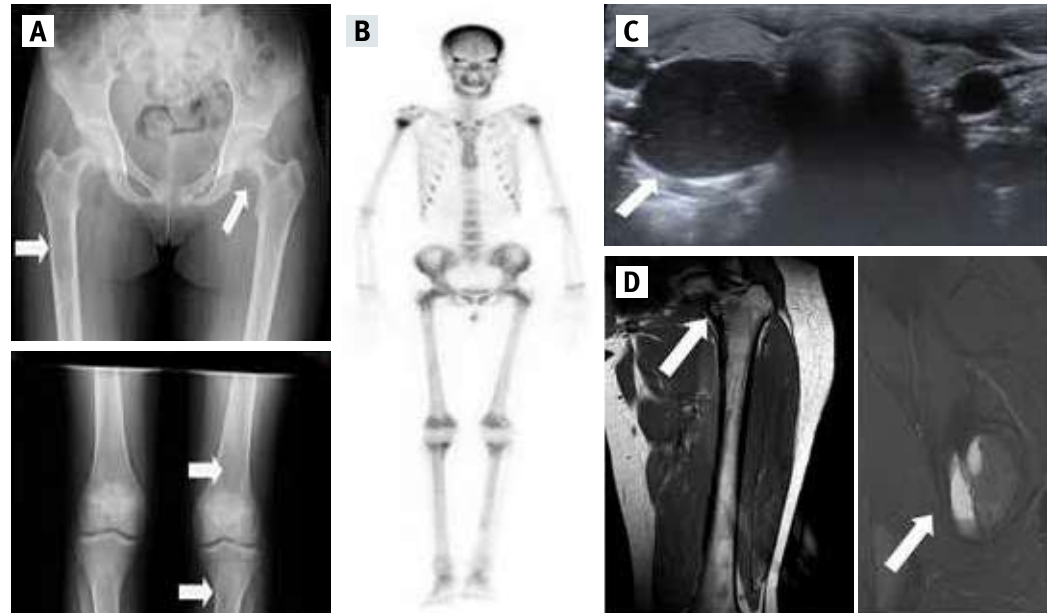
- **X-ray of lower limbs:** Multiple lytic lesions in bones of the lower limbs were noted [Figure 1A]
- **Biochemistry:** Laboratory results included serum calcium 11.9 mg/dl (normal range 8.4–10.4), phosphorous 3 mg/dl (normal range 2.5–5), alkaline phosphatase 2435 U/L (normal range 47–119), 75% bone isoenzyme (normal range 62–100%). Serum 25-OH Vitamin D 19 nmol/L (< 25 deficiency, range 75–125), 1,25-OH-vitamin D: 289 pmol/L (range 39–160), PTH 1881 pg/ml (range 14–72), and TSH 1.91 uIU/ml (range 0.39–4) were measured. Other electrolytes and kidney functions were within the normal range. Ca/Cr clearance ratio in a 24-hour urine collection was 0.5 (above the 95th percentile for age)
- **Other imaging studies:** Bone scan (Tc-99m) demonstrated diffuse hypermetabolic bone [Figure 1B]. Technetium (<sup>99m</sup>Tc) sestamibi scan showed a hyperintense spot on the right lower pole of

the thyroid. Neck ultrasound revealed a hypoechogenic lesion 2.6 × 1.6 × 1.9 cm in the right lower pole of the thyroid gland and otherwise normal thyroid, parotid, and saliva glands [Figure 1C]. These findings were compatible with a single parathyroid adenoma

## HOSPITAL COURSE

During the diagnostic workup the patient developed symptomatic hypercalcemia of 13.3 mg/dl. She was treated with an infusion of NaCl 0.9% and intravenous furosemide. Prior to parathyroidectomy, she was treated with vitamin D 5000 IU/day, and 60 mg pamidronate was given intravenously as a single dose. Serum calcium levels stabilized at 11.1–12.2 mg/dl and the patient underwent parathyroidectomy one week later. During surgery, an enlarged gland at the right lower pole of the thyroid was removed. The pathology report indicated a parathyroid adenoma. After surgery, PTH levels decreased to 229 pg/ml and asymptomatic hypocalcemia (7.4 mg/dl) occurred in the first 72 hours. Oral calcium supplementation was added, and the patient was discharged 4 days later with continued vitamin D and oral calcium supplementation at home. Six months after surgery, the patient continued to complain of limb pain, most probably due to non-compliance with vitamin D therapy. A magnetic resonance imaging (MRI) performed at that time showed Brown tumors in the femur [Figure 1D]. During the first year post-surgery, calcium levels remained normal (8.8–10 mg/dl), and PTH decreased to 101 pg/ml.

**Figure 1.** Imaging of a 15-year-old patient diagnosed with primary hyperparathyroidism and vitamin D deficiency [A] X-ray showing multiple lytic lesions (arrows) [B] Technetium ( $^{99m}\text{Tc}$ ) bone scan showing diffuse hypermetabolic bones [C] neck ultrasound showing hypoechogenic lesion  $2.6 \times 1.6 \times 1.9$  cm in the right lower pole of the thyroid gland (arrow) [D] lower extremity magnetic resonance imaging compatible with osteitis fibrosa cystica or brown tumors (arrows)



## COMMENT

Symptoms of hyperparathyroidism in children are usually vague and include bone and abdominal pain. Up to 85% are symptomatic at diagnosis and most of the patients show skeletal or renal pathology [1]. Our patient presented with bone pain due to multiple lytic lesions, which is the main clinical feature of hyperparathyroidism in children. Elevated PTH in combination with elevated ALP and hypophosphatemia are well recognized findings in vitamin D deficiency.

The majority of PHPT adult patients have concomitant vitamin D deficiency. This finding is in contrast to the pediatric population, in which there are only a few case reports describing the association of vitamin D deficiency rickets and parathyroid adenoma. In southern Israel, vitamin D deficiency is very common among Bedouin women. Rudoy and Volkov [2] reviewed 202 medical records of women of childbearing age undergoing vitamin D testing. None of the subjects had normal or even near-normal 25-OH vitamin D levels and many complained of musculoskeletal pain. The extremely high prevalence of vitamin D deficiency in this population can be explained by a combination of socio-demographic factors, including continued dress with traditional clothing that affords

minimal skin exposure, urbanization with reduced outdoor activity, and an increased consumption of phytates compared to the traditional diet.

After parathyroidectomy, serum calcium levels decrease. The hypocalcemia is usually mild and reaches a nadir 2 to 4 days after surgery. This result occurs because the normal parathyroid tissue is suppressed by the adenoma. The hypocalcemia can persist longer if all four of the glands are removed or injured accidentally during the procedure.

## HUNGRY BONE SYNDROME

Hungry bone syndrome (HBS) refers to profound and prolonged hypocalcemia starting 4 days after parathyroidectomy and is associated with hypophosphatemia and hypomagnesemia. In children, the risk for HBS is approximately 50% [1]. The condition occurs more often in patients with severe primary hyperparathyroidism and preoperative high bone turnover manifested as Brown tumors. One mechanism that has been proposed is that decreasing levels of PTH result in arrest of bone reabsorption and continued bone formation. This condition causes an increased influx of calcium to the bone at the remodeling sites.

There are only a few case reports in the literature regarding HBS in the pediatric

population and most of them describe adolescents [3]. The accelerated growth associated with high bone turnover during puberty may explain the increased risk. Management of HBS includes giving large amounts of calcium intravenously and then orally as soon as possible, magnesium supplements, and active metabolites of vitamin D (calcitriol/alfacalcidol) [4]. For many years, active vitamin D metabolite has been given preoperatively to prevent HBS, because vitamin D depletion was considered a risk factor for HBS. The evidence regarding the benefit of this treatment is questionable and the current recommendations are to treat patients after parathyroidectomy as needed [5].

Bisphosphonates inhibit the action of osteoclasts and absorption of the bone. The successful use of bisphosphonate, such as pamidronate or zoledronate, for primary prevention of HBS in patients with hyperparathyroidism after parathyroidectomy is described in adults. Currently, these drugs are used in children with osteogenesis imperfecta and osteoporosis as well as for the treatment of acute hypercalcemia. Our patient received one dose of preoperative pamidronate to decrease calcium levels and enable vitamin D therapy. We speculate that although the patient had multiple risk

factors for developing HBS, the perioperative combination therapy of vitamin D and pamidronate prevented the occurrence of clinically significant HBS.

### CONCLUSIONS

To the best of our knowledge, this is the first report of perioperative pamidronate use and possible prevention of HBS in a patient with concomitant parathyroid adenoma and vitamin D deficiency in the pediatric age group.

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### Capsule

#### Frequent mutations that converge on the NFKBIZ pathway in ulcerative colitis

Chronic inflammation is accompanied by recurring cycles of tissue destruction and repair and is associated with an increased risk of cancer. However, how such cycles affect the clonal composition of tissues, particularly in terms of cancer development, remains unknown. **Kakiuchi** and colleagues showed that in patients with ulcerative colitis, the inflamed intestine undergoes widespread remodelling by pervasive clones, many of which are positively selected by acquiring mutations that commonly involve the *NFKBIZ*, *TRAF3IP2*, *ZC3H12A*, *PIGR*, and *HNRNPF* genes and are implicated in the downregulation of IL-17 and other pro-inflammatory signals. Mutational profiles vary substantially between colitis-associated cancer and non-dysplastic tissues in ulcerative colitis, which indicates that there are distinct mechanisms of positive selection in both tissues. In particular, mutations

in *NFKBIZ* are highly prevalent in the epithelium of patients with ulcerative colitis but rarely found in both sporadic and colitis-associated cancer, indicating that *NFKBIZ*-mutant cells are selected against during colorectal carcinogenesis. In further support of this negative selection, the authors found that tumor formation was significantly attenuated in *Nfkbiz*-mutant mice and cell competition was compromised by disruption of *NFKBIZ* in human colorectal cancer cells. These results highlight common and discrete mechanisms of clonal selection in inflammatory tissues, which reveal unexpected cancer vulnerabilities that could potentially be exploited for therapeutics in colorectal cancer.

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Eitan Israeli

### Capsule

#### Human and mouse single-nucleus transcriptomics reveal TREM2-dependent and TREM2-independent cellular responses in Alzheimer's disease

Glia have been implicated in Alzheimer's disease (AD) pathogenesis. Variants of the microglia receptor triggering receptor expressed on myeloid cells 2 (TREM2) increase AD risk, and activation of disease-associated microglia (DAM) is dependent on TREM2 in mouse models of AD. **Zhou** et al. surveyed gene-expression changes associated with AD pathology and TREM2 in 5XFAD mice and in human AD by single-nucleus RNA sequencing. The authors confirmed the presence of *Trem2*-dependent DAM and identified a previously undiscovered *Serpina3n*+*C4b*+ reactive oligodendrocyte population in mice. Interestingly, remarkably different glial phenotypes were evident in human AD. Microglia signature

was reminiscent of IRF8-driven reactive microglia in peripheral-nerve injury. Oligodendrocyte signatures suggested impaired axonal myelination and metabolic adaptation to neuronal degeneration. Astrocyte profiles indicated weakened metabolic coordination with neurons. Notably, the reactive phenotype of microglia was less evident in *TREM2*-R47H and *TREM2*-R62H carriers than in non-carriers, demonstrating a TREM2 requirement in both mouse and human AD, despite the marked species-specific differences.

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### "A man may die, nations may rise and fall, but an idea lives on"

John Fitzgerald Kennedy (1917–1963), 35th American President, served from 1961 until his assassination in 1963