Drug-Induced PTH Resistance

Hemmet Al Haddad[1], Manal Abu Farha[2], Alaa AbdAllah Salah[3], Mirette Makram[4] Abanoub Edwar Moussa Khalil[5], Ahmed Fayed[6]*

1) Professor of Endocrinology and Internal Medicine, Faculty of Medicine, Cairo University

2) Professor of Hematology and Internal Medicine, Faculty of Medicine, Cairo University

3) Assistant lecturer of Internal Medicine, Faculty of Medicine, Cairo University

4) Assistant lecturer of Endocrinology and Internal Medicine, Faculty of Medicine, Cairo University

5) Resident of Internal medicine, Faculty of medicine, Cairo University

6) Professor of Nephrology and Internal medicine, Faculty of medicine, Cairo University

Background

PTH acts by binding to the PTH type 1 receptor (PTH1R) that leads to activation of the $G_s\alpha$ and intracellular cyclic adenosine monophosphate (cAMP) production, leading to a decrease in phosphate reabsorption, synthesis of the active form of vitamin D (1,25-dihydroxyvitamin D) and an increase in calcium reabsorption.

The historical classification of PTH resistance relies mainly on the division of pseudohypoparathyroidism into maternally inherited pseudohypoparathyroidism type 1A (PHP1A) and paternally inherited pseudohypoparathyroidism type 1B (PHP1B); however, the growing knowledge on the PTH/PTHrP signaling pathway has allowed the understanding of different related disorders characterized by PTH resistance, including drug-induced PTH resistance, autoimmune diseases and hypomagnesemia.

Examples of drugs that can cause PTH resistance are Lithium, antiresorptive drugs, and Mg-depleting drugs as cisplatin and loop diuretics.

Case presentation

25 years male who was apparently healthy with history of NSAIDS, gabapentin and vitamin D intake for lower backache two weeks before presentation, followed by spontaneously resolved priapism two days before presentation, presenting with acute onset of confusion not preceded by seizures, headache, neck stiffness, fever or trauma.

Physical examination

GCS 13/15, BP: 145/90 mmHg, Pulse: 107 b/m, RR 28/min, Temperature: 36.9°C

Neurological examination: Slurred speech, signs of cerebellar involvement, including intention tremors on finger-to-nose testing. No papilledema on fundus examination. Cranial nerves, motor strength, tone, reflexes, and sensory modalities were intact.

Cardiac examination: unremarkable apart from accentuated S1/S2.

Abdominal and chest examination: unremarkable.

Investigations

CBC showed normocytic normochromic anemia (hb 7.8), normal liver functions.

Kidney functions showed acute renal failure, probably secondary to rhabdomyolysis:

Serum creatinine 8.28 mg/dl, urea 303 mg/dl, k 3.3 mmol/l, PH:7.19 HCO3:6.5 CK: 3613, A/C ratio: 2.62 mg/mg.

PTH: 641 pg/ml, serum calcium: 5 mg/dl, Phosphorus: 7.9 mg/dL, 25 OH Vit D: 44.1 ng/mL

Immunology profile: ANA 1/80, Anti-cardiolipin Abs and Anti B2 glycoprotein Abs are negative.

Pelviabdominal ultrasound: Bilateral grade II-III pathological kidney, with poor corticomedullary differentiation, RT kidney is 9.3 x 4.2 cm, LT kidney is 9.1 x 4.1 cm.

Parathyroid ultrasound: No hyperplasia.

MRI brain: Bilateral symmetrical patchy areas of limited diffusion seen at fronto-parietal and parieto-occipital areas, a small focus at the left cerebellar hemisphere, likely an old infarct.

Skeletal survey: No abnormalities detected with good bone marrow density.

Management and follow-up

The patient received hemodialysis sessions with consequent improvement of his conscious level, neurological deficits and metabolic acidosis.

After one month of regular hemodialysis and oral calcium supplementation, serum calcium normalized (9.5 mg/dl) and phosphorus dropped (1.9 mg/dl), as well as the PTH level (125 pg/mL), in a few weeks only.

Discussion

The priapism occasionally happens with severe uremia and metabolic acidosis or as a result of sympathomimetic drug abuse as well as the neurological deficits that may be attributed to sympathomimetic intake or uremia or accumulation of gabapentin due to its non-renal adjustment in a patient with chronic kidney disease.

However, the absence of signs of severe chronic hypocalcemia (good bone marrow density, absent parathyroid hyperplasia on neck ultrasonography, no basal ganglia calcification nor cataract) favors acute onset of severe hypocalcemia beside the rapid improvement of calcium, phosphorus and PTH levels in the context of drug induced rhabdomyolysis causing acute on top of chronic kidney injury has led to the suspicion of drug induced PTH resistance, that resolved upon stopping of the offending drugs causing the rapid improvement of serum calcium level, phosphorus and PTH, rather than merely secondary hyperparathyroidism.

Conclusion

The growing knowledge on the PTH/PTHrP signaling pathway allowed the understanding of different related disorders characterized by PTH resistance, including drug induced PTH resistance that should be suspected in the acute onset and offset of hypocalcemia and hyperparathyroidism upon stopping the offending drugs. Recognition of drug-induced PTH resistance needs high clinical suspicion, as it affects the prognosis as well as the treatment strategy.

Keywords

Severe hypocalcemia, bone marrow density, drug drug-induced PTH resistance.