An interesting case of primary hypoparathyroidism

D. A. Kirpalani, J. Patel, H. Shah, A. Kirpalani, D. Amrapurkar, R. Choudhary, A. Dhurve

Department of Nephrology and Gastroenterology, Bombay Hospital Institute of Medical Sciences, Mumbai, Maharashtra, India

ABSTRACT

Primary hypoparathyroidism can occur due to an activating mutation of calcium sensing receptor (CaSR). Most patients remain asymptomatic and therefore not diagnosed until adulthood. We present a 38-year-old lady who had a history of muscle cramps since 8 years. She presented with vomiting, abdomen pain and body ache, showed clinical evidence of hypovolemia, severe hypocalcemia, hypokalemia, hypomagnesemia, hyperphosphatemia and metabolic alkalosis. Her 24 h urinary phosphorus was low and 24 h urinary excretion of sodium, potassium and chloride were high. Her intact parathormone was on the lower side of the normal range. She improved once we had corrected her biochemical abnormalities. By excluding acquired causes of hypoparathyroidism, we are able to conclude that this may be a case of primary hypoparathyroidism due to activating mutation of CaSR.

Key words: Calcium sensing receptor, primary hypoparathyroidism, hypocalcemia

Introduction

Primary hypoparathyroidism can occur due to an activating mutation of calcium sensing receptor (CaSR).[1] Patients are usually asymptomatic and therefore they are not diagnosed until adulthood, when hypocalcemia is incidentally noted.[2] A few patients, however, have symptomatic hypocalcaemia; children in particular become symptomatic with seizures and tetany during periods of stress such as a febrile illness and may be mislabeled as having febrile seizures. Biochemically, these patients have hypocalcemia, hypomagnesemia, normal or only slightly low serum intact parathormone (iPTH) concentrations, high or high normal urinary calcium concentration and occasionally, recurrent nephrolithiasis and/or nephrocalcinosis, particularly during treatment with vitamin D supplementation. Some patients also have potassium wasting with hypokalemia and metabolic alkalosis, creating a phenotype similar to Bartter syndrome. These patients appear to have a more marked gain of function in the CaSR than those without hypokalemia.[3] We present an interesting case of hypocalcemia due to hypoparathyroidism who presented in adulthood.

Address for correspondence:
Dr. Dilip A. Kirpalani, 108/102, Lady Ratan Tata Medical and Research Centre, Maharshi Karve Road, Cooperage,
Mumbai - 400 021, Maharashtra, India.
E-mail: dkirpalani@hotmail.com

Access this article online	
Quick Response Code:	Website: www.indianjnephrol.org
	DOI: 10.4103/0971-4065.132018

Case Report

A 38-year-old lady presented in February 2013, with history of persistent vomiting, abdominal pain and generalized body ache since 2 weeks. She had been diagnosed with moderately differentiated cholangiocarcinoma in June 2011, for which she had undergone partial hepatectomy with bile duct resection with cholecystectomy. She also gave a history of recurrent muscle cramps since last 8 years, for which she had been taking calcium supplements intermittently. There was a history of unspecified neonatal illness needing neonatal intensive care unit admission for 10 days immediately after her birth. She also had childhood bronchial asthma with recurrent respiratory tract infections. She has two otherwise healthy children, one of whom had a history of recurrent lower respiratory tract infections. She has one healthy sibling, 31-year-old male; she had a sister who expired 25 days after birth (medical details not available).

On clinical examination, patient was conscious, oriented, afebrile but showed clinical evidence of volume

contraction – skin turgor was lost and there was dryness of mucous membranes. Blood pressure was 90/60 mm of Hg with 20 mm of Hg postural drop in systolic blood pressure. Systemic examination was unremarkable. There was no clinical evidence of hypocalcemia.

Investigations were as shown in Table 1. Significantly, arterial blood gas analysis was as follows: pH 7.45, pCO_2 24 mm Hg, pO_2 95 mm Hg, HCO_3 28 meq/ l, suggestive of combined metabolic alkalosis and respiratory alkalosis (respiratory alkalosis related to tachypnea due to severe pain). She was started on intravenous calcium gluconate, Intravenous magnesium sulfate and tablet calcium acetate as a phosphate binder, tablet calcitriol and intravenous fluids. In view of severe hypocalcemia, hypomagnesaemia, hyperphosphatemia and relatively low iPTH, a provisional diagnosis of primary hypoparathyroidism was considered. Investigations were further carried out as shown in Table 2.

With intravenous correction, her serum calcium increased to 6.5 mg/dl, serum magnesium increased to 1.6 mg/ dl and serum potassium increased to 3.2 mg/dl. Serum phosphorus reduced to 4.6 mg/dl. Calcium acetate was continued, dose of calcitriol was reduced to 25% of the original dose (from 1.0 μg/day to 0.25 μg/day) and patient was started on T. magnesium orotate - 1.5 g/ day and oral potassium chloride syrup. Intravenous replacement of calcium, magnesium and potassium were discontinued. Her symptoms of body ache and abdominal pain remarkably subsided. She was discharged from the hospital and advised to continue oral supplements of calcium, magnesium and potassium and to follow-up with us on a monthly basis.

Table 1: Hematology and biochemistry investigations

Investigations	Investigations
Hb-12.0 g/dl	S. total protein-7.4 g/dl
TLC-5900/cu.mm	S. albumin-4.0 g/dl
Platelet count-2.05lac/cu.mm	S. calcium-4.7 mg/dl
S. Creatinine-0.8 mg/dl	S. ionised calcium-2.0 mg/dl
Bl. Urea-8 mg/dl	S. phosphorus-7.1 mg/dl
S. Na^+-134 meq/dl	S. uric acid-2.3 mg/dl
S. K^+-2.8 meq/dl	S. magnesium-0.7 mg/dl
S. Cl^--93 meq/dl	iPTH-23.8 pg/ml
Venous bicarbonate-28 meq/l	S. 25(OH) vitamin D-27.0 ng/ml
S. Bilirubin-0.8 mg/dl	Urine analysis-unremarkable
SGPT/SGOT-normal	S. amylase and S. lipase-normal
Random blood sugar-normal	

Hb: Hemoglobin, TLC: Total leukocyte count, S. creatinine: Serum creatinine, SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic-pyruvic transaminase, S. bilirubin: Serum bilirubin, S. total protein: Serum total protein, S. albumin: Serum albumin, S. calcium: Serum calcium, S. Ionised calcium: Serum ionised calcium, S. Phosphorus: Serum phosphorus, S. uric acid: Serum uric acid, S. magnesium: Serum magnesium, iPTH: Intact parathormone, S. 25(OH) vitamin D: Serum 25-hydroxy vitamin D, S. amylase: Serum amylase, S. lipase: Serum lipase

Discussion

Our patient is a case of hypocalcemia due to hypoparathyroidism. Her symptoms of hypocalcemia and hypomagnesemia started in adulthood and were aggravated by a stressor, i.e., surgery for cholangiocarcinoma. She also had features of Bartter syndrome, namely, hypokalemia and metabolic alkalosis. She had a low normal iPTH level which goes in favor of primary hypoparathyroidism because serum iPTH level was relatively low in the setting of moderate to severe hypocalcemia. She had the triad of hypocalcemia, hyperphosphatemia and hypoparathyroidism, which goes in favor of primary hypoparathyroidism. The hypocalcemia, hyperphosphatemia, hypokalemia and hypomagnesemia all responded to therapy.

She had a normal urinary calcium excretion. Classically hypercalciuria is more frequent in such patients. Some of these patients can have normal calcium excretion and may become hypercalciuric only when supplemented with vitamin D.[4,5]

The differential diagnosis of hypoparathyroidism includes post-surgical ablation of parathyroid glands, autoimmune diseases and abnormal parathyroid gland development (genetic defects).

Table 2: Special Investigations

Investigation	Result
Thyroid function and S. cortisol	Normal
S. CPK and S. lactate	Normal
ANA, anti-Thyroid Peroxidase antibody, anti-intrinsic factor antibody, anti-parietal cell antibody	All negative
24 h urinary volume	1600 ml
24 h urinary calcium	90 mg/1600 ml (normal range is 50-200 mg/24 h)
24 h urinary phosphorus	438 mg/1600 ml (normal range is 500-1500 mg/24 h)
24 h urinary sodium	301 meq/1600 ml (normal range is 129-215 meq/24 h
24 h urinary potassium	415 meq/1600 ml (normal range is 25-100 meq/24 h)
24 h urinary chloride	2128 meq/1600 ml (normal range is 196-420 meq/24 h)
S.1, 25(OH) 2 vitamin D3	51 pg/ml (normal range is 19.6-54.3 pg/ml)
Renal sonography	Unremarkable with no evidence of nephrocalcinosis
CT scan of brain	Bilaterally symmetrical basal ganglia and cerebellar calcification
Whole body PET-CT	No other evidence of abnormal calcification

S. cortisol: Serum cortisol, S. CPK: Serum creatinine phosphokinase, S. lactate: Serum lactate, ANA: Antinuclear antibody, anti-TPO: Antithyroperoxidase, CT: Computed tomography, PET: Positron emission tomography

We ruled out various autoimmune causes of hypopar athyroidism in our patient such as: (1) autoimmune polyendocrinopathy candidiasis ectodermal dystrophy and (2) other autoimmune diseases, as her antinuclear antibody was negative, anti-thyroid peroxidase antibody was negative, anti-parietal cell antibody and anti-intrinsic factor antibody were also negative. There was no history of any surgery on parathyroid or thyroid glands. After excluding all these conditions, we consider a diagnosis of primary hypoparathyroidism due to activating (gain of function) mutation of the CaSR gene as the most likely cause of her illness. Due to financial constraints of the patient, we were unable to subject our patient to mutational analysis of the CaSR gene.

Primary hypoparathyroidism, which occurs due to an activating (gain of function) mutation of the CaSR gene shifts the calcium-PTH curve to the left and decreases the set point of the CaSR, so that PTH is not released at the serum calcium concentrations that normally trigger PTH release, thereby causing hypocalcemia. As a result of this, low serum calcium is perceived as normal, leading to a downward resetting of the PTH-calcium relationship. In patients with primary hypoparathyroidism due to CaSR abnormality, serum PTH concentrations are low or inappropriately normal despite the presence of mild to moderate and occasionally, severe hypocalcemia.[6] In contrast to other causes of hypocalcemia, urinary calcium excretion is normal or overtly high in the untreated state; presumably due to increased activation of CaSR in the kidney. The goal of treatment in such a patient is to maintain serum calcium in the low normal range in order to alleviate symptoms, but to avoid normocalcemia which may result in hypercalciuria. This can be achieved with cautious calcium and vitamin D supplementation along with monitoring of urinary calcium excretion. If hypercalciuria is present, calcitriol supplementation is avoided or discontinued (if already being given) and judicious use of a thiazide diuretic may be beneficial.[7]

By excluding acquired causes of hypoparathyroidism, we were able to conclude that our patient may be a case of primary hypoparathyroidism due to activating mutation of CaSR.

References

1. Pollak MR, Brown EM, Estep HL, McLaine PN, Kifor O, Park J, *et al*. Autosomal dominant hypocalcaemia caused by a Ca (2+)-sensing receptor gene mutation. Nat Genet 1994;8:303-7.
2. D'Souza-Li L, Yang B, Canaff L, Bai M, Hanley DA, Bastepe M, *et al*. Identification and functional characterization of novel calcium-sensing receptor mutations in familial hypocalciuric hypercalcemia and autosomal dominant hypocalcemia. J Clin Endocrinol Metab 2002;87:1309-18.
3. Lienhardt A, Bai M, Lagarde JP, Rigaud M, Zhang Z, Jiang Y, *et al*. Activating mutations of the calcium-sensing receptor: Management of hypocalcemia. J Clin Endocrinol Metab 2001;86:5313-23.
4. Egbuna OI, Brown EM. Hypercalcaemic and hypocalcaemic conditions due to calcium-sensing receptor mutations. Best Pract Res Clin Rheumatol 2008;22:129-48.
5. Pearce SH, Williamson C, Kifor O, Bai M, Coulthard MG, Davies M, *et al*. A familial syndrome of hypocalcemia with hypercalciuria due to mutations in the calcium-sensing receptor. N Engl J Med 1996;335:1115-22.
6. Brown EM. Clinical lessons from the calcium-sensing receptor. Nat Clin Pract Endocrinol Metab 2007;3:122-33.
7. CaSRdb. Calcium sensing receptor database. Available from: http://www.casrdb.mcgill.ca. (FIH- (OMIM entry 146200).

How to cite this article: Kirpalani DA, Patel J, Shah H, Kirpalani A, Amrapurkar D, Choudhary R, *et al*. An interesting case of primary hypoparathyroidism. Indian J Nephrol 2014;24:175-7.

Source of Support: Nil, **Conflict of Interest:** None declared.