Isolated PTH Renal Resistance Pseudohypoparathyroidism 1b: A Rare Cause of Hypocalcemia

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ABSTRACT

A case of Pseudohypoparathyroidism 1b is reported, who presented with signs and symptoms of hypocalcemia. Causes, diagnosis and management with new insight into genetic novel mutations in PHP are discussed. The objectives are to provide information regarding problems of Calcium balance, causes and making diagnosis of pseudohypoparathyroidism, learn complexities of PTH cellular interactions and calcium homeostasis and learn the genetic novel mutations of various types of PHP.

Keywords: *hyperphosphatemia; hypocalcemia Isolated PTH resistance; pseudohypoparathyroidism; secondary hyperparathyroidism.*

INTRODUCTION

Hypocalcemia is a commonly encountered problem in the inpatient hospital setting and often in the outpatient setting as well. It may be detected as just an asymptomatic biochemical abnormality or may present as a life-threatening situation. Etiologies of hypocalcemia include problems with absorption of calcium, defects of the calcium sensing receptor, end organ resistance or excessive loss. We, hereby, present an interesting case of a young female with symptomatic hypocalcemia who was diagnosed to have a very rare cause for hypocalcemia – pseudohypoparathyroidism type 1b.

CASE REPORT

A 23 year old female without significant past history presented to the hospital with complains of tingling and numbness of the hands and feet, increased fatigue and muscle weakness for 2 days. All her symptoms were increased with exertion and heavy physical workout. There was no history of any other significant medical illness, malabsorption or any drugs like steroids, thyroxine, anticoagulants etc. Her nutritional intake was adequate. General physical and systemic examination was unremarkable. Initial investigations on admission revealed hypocalcemia [Mean calcium of 5.2mg/dl (N- 9-11 mg/dl)], Ionised Ca - 0.80mmol/l , Magnesium -1.7meq/l (N-1.5-3.0meq/l) , K- 2.3mmol/l, Albumin- 4.2g/dl, Phosphorus -7.2mg/dl (N- 3-5 mg/dl),Parathyroid hormone (PTH) -315pg/ml (N-7-52 pg/ml), Vit D 1,25 Dihydroxy cholecalciferol – 30pg/ml. Urine calcium was 1.2 mg/dl and phosphorus ≤ 10 mg/dl. EKG revealed sinus arrhythmia with prolonged QTc interval. Chest X-ray, Computerized tomograhic (CT) scan of abdomen and magnetic resonance imaging

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(MRI) brain were normal. Since the patient had a low calcium level, high PTH, high phosphorus and a normal Vitamin D 1, 25 Dihydroxy cholecalciferol level, it was suggestive of a PTH-resistance state. The diagnosis of Pseudohypoparathyroidism (PHP) was made on the basis on hypocalcemia, hyperphosphatemia and elevated parathyroid hormone in the presence of normal renal function and normal magnesium levels. In the absence of short 4th/5th metacarpals, obesity and round facies, she was classified as Pseudohypoparathyroidism Type 1b (PHP 1b). She was treated with intravenous Calcium Gluconate, Magnesium, Vitamin D (Calcitriol 0.25) and placed on low phosphorous diet alongwith telemetry monitoring. Endocrine service was consulted and they recommended adding phosphate binders to the treatment regimen. Her calcium level started to raise slowly, phosphorous level was also trending down. Investigations at discharge showed a Calcium of 7.6mg/dl, Ionised calcium - 0.92mmol/l, Phosphorus-5.2mg/dl, PTH- 116pg/ml, Vit D, 1, 25 DiHydroxy cholecalciferol – 68pg/ml. She gradually started to feel better and was symptom free at time of discharge. Discharge medications included calcium citrate 1900 mg TID, elemental calcium 1200 mg, and Calcitriol 1mcg daily with follow-up as an outpatient.

Table 1. Biochemical Profile.

Serum Biochemistry	Pre-treatment	Post-treatment
Calcium (8.4 – 10.2) mg/dL	5.2	7.6
Magnesium (1.3 – 2.1) meq/L	1.6	1.6
Phosphorus (2.7 – 4.5) mg/dl	7.2	5.2
Calcium, Ionized (1.13-1.32) mmol/L	0.80	0.92
Albumin (3.4-4.8) g/dL	4.2	4.7
Alk. Phos (34 – 104) U/L	112	110
PTH Intact (15-65) pg/mL	315	116
TSHS (0.270-4.200) miu/ml	3.8	3.8
Vit D 1,25 (OH)D pg/ml	30	68

DISCUSSION

Calcium homeostasis is maintained by Parathyroid hormone (PTH), active vitamin D 1, 25. Isolated renal resistance to the effects of PTH, as in our case, is a very rare cause of hypocalcemia. Pseudohypoparathyroidism (PHP) is a rare heterogeneous group of genetic disorders linked to dysfunctional G proteins especially Gs alpha subunit. In one study in Japan the prevalence was found to be 3.4 cases per 1 million people but no information is available regarding the prevalence of PHP in the rest of the world.[1] PHP is characterized by hypocalcemia, hyperphosphatemia, an increased serum concentration of PTH. Clinical and laboratory findings are of hypoparathyroidism but with high levels of PTH in the absence of chronic renal failure or magnesium deficiency. There is end- organ insensitivity to the biologic activity of PTH. Administration of exogenous PTH fails to produce expected phosphaturia or stimulate renal production of cAMP. PHP is classified into type I and II with further subdivision of type I into Ia, Ib and Ic depending on the molecular defects in the gene GNAS 1.[2]

Patients with the type 1b PHP have hypocalcemia, hyperphosphatemia and high PTH but do not have Albright hereditary osteodystrophy phenotype because the PTH resistance is confined to the kidney in this disorder. The patient usually presents with varying signs and symptoms of hypocalcemia like paresthesias, muscular cramping, tetany, carpopedal spasm, or seizure. Biochemical parameters are suggestive of PTH resistance. Imaging modalities include radiography to see bony changes and soft tissue opacities, CT scan to rule out ossification of basal ganglia. ECG shows prolonged QTc interval. Modified Ellsworth Howard test can be carried to differentiate between PHP1b and PHP2.[3] The condition needs to be differentiated from vitamin D deficiency, secondary hyperparathyroidism and autoimmune polyglandular syndromes. The goals of drug treatment are to correct calcium deficiency, to prevent complications, and to reduce morbidity. Administration of oral calcium and 1alpha-hydroxylated vitamin D metabolites, such as calcitriol, remains the mainstay of treatment in PHP. The other forms of vitamin D are not used in PHP 1b as PTH resistance at proximal convoluted tubules (PCT) does not allow synthesis of 1,25 (OH) 2D from 25-OH D. Intravenous calcium is the initial treatment for all patients with severe symptomatic hypocalcemia , and monitoring is needed for any adverse cardiac effects. Target is to achieve mid to high normal range serum calcium levels, suppression of PTH to normal and to avoid hypercalciuria. Hypercalciuria as a result of calcitriol and calcium therapy is not a cause of concern in PHP1b as there is PTH resistance in distal convoluted tubules, hence the effect is functional. The monitoring of PTH levels is needed to maintain it within normal range as signs of hyperparathyroid bone disease may occasionally develop (osteitis fibrosa cystica) due to unimpaired PTH responsiveness in bone. In the event of development of tertiary hyperparathyroidism and hyperparathyroid bone disease not suppressed by sufficient calcium and active

vitamin D, parathyroidectomy may remain the ultimate treatment. Ocular assessment is advised for cataract detection.

Type 1b PHP is a rare autosomal dominant disorder, appears to be caused by mutations that affect the regulatory elements of GNAS1 (a gene encoding the alpha subunit of the G protein, coupled to the PTH receptor). A novel mutation identified in the carboxyl terminus of gene GNAS 1 was reported in 3 patients with PHP 1b.[4] The mother and maternal grandfather carrying the same mutation were clinically unaffected. This may explain the paternal imprinting of the GNAS 1 gene.[5,6] This mutation may cause the inability to support GS expression in kidney and not in the other tissues thereby explaining renal resistance to PTH in these patients. PHP usually presents at an early age but PHP1b has been reported as late as 46 years of age[7]. About 50% cases of PHP1b are sporadic so family history of similar illness may not be there and the risk to subsequent generations is difficult to quantify.

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