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*International Journal of Current Research in Life Sciences*
*Vol. 10, No. 02, pp.3417-3420, February, 2021*

**ISSN: 2319-9490**

# RESEARCH ARTICLE

## BARTTER TYPE V: A CALCIUM SENSING RECEPTOR ACTIVATING MUTATION

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**Received 27th December, 2020; Accepted 20th January, 2021; Published 28th February, 2021**

## ABSTRACT

Hypoparathyroidism, a rare disorder characterized by hypocalcemia and hyperphosphatemia, has been attributed to many causes. When the culprit is an activated mutation of the calcium sensing receptor which is also expressed in the kidney, it can be associated with Bartter phenotype: hypokalemia, hypomagnesemia and metabolic alkalosis. We report a case of a 59-year-old female patient recently diagnosed with Parkinson disease who presented with generalized tonic-clonic seizures. The patient was found to have severe hypocalcemia with the salt-losing phenotype and improved after repletion with calcium, potassium, magnesium and vitamin D. After excluding other causes of primary hypoparathyroidism, the patient was found to have late onset presenting Bartter type V syndrome. This case report helps understand the pathophysiology, clinical presentation and treatment of Bartter type V syndrome; it also helps establish the fact that it is an endocrine disorder.

***Key words:*** Hypoparathyroidism, hypocalcemia, calcium sensing receptor, Bartter type 5 syndrome



**Citation:** ***Salwa Nassif Azar, Patrick Charbel Sarkis, Akram Salim Echtay and Mohamad Souheil El Rawas*****. 2021.** "Bartter type V: A calcium sensing receptor activating mutation" *International Journal of Current Research in Life Sciences*, 10, (02), 3417-3420.

## INTRODUCTION

Primary hypoparathyroidism is a rare disorder characterized by hypocalcemia, hyperphosphatemia and inappropriately low or normal intact parathyroid hormone (PTH) levels or high PTH levels in the case of pseudohypoparathyroidism (Shoback, 2008). Most cases are acquired with anterior neck surgery being responsible for 75% of cases, followed by autoimmune diseases, affecting either the parathyroid glands alone or multiple other endocrine glands (1) and less frequently, rare disorders infiltrating the parathyroids such as metastatic disease, iron or copper overload or by ionizing radiation exposure (Clarke, 2016). The remainder is caused by genetic etiologies many of which have established genetic defects: the autoimmune polyendocrinopathy syndrome type 1, Di- George syndrome, hypoparathyroidism-deafness- renal dysplasia syndrome, Kenny-Caffey syndrome type 1 and 2 and many others (Shoback, 2016).

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Of the non-syndromic genetic forms are molecular defects causing isolated hypoparathyroidism which include mutations in the PTH gene, transcription factor GCM2, calcium sensing receptor (CaSR), GA11 and SOX3 (Favus, 2006). Activating mutations of the CaSR result in autosomal dominant hypocalcemia and Bartter syndrome type 5 (Hebert, 1996).

**Case presentation:** A 59-year-old female patient, presented to the emergency department in June 2019 for generalized tonic-clonic seizures after two weeks of persistent vomiting and decreased per os intake. Family members state that the episodes had been occurring for the past 3 months. The patient has a history of hydrocephalus treated with a lumboperitoneal shunt 20 years ago. She also developed dementia and unsteady shuffling gait five months prior to presentation, after which she was diagnosed with Parkinson disease and started on Carbidopa/levodopa 25/250mg twice daily. Seizures were first controlled with intravenous midazolam and valproic acid. Patient's blood pressure was 90/60 mmHg, vital signs were otherwise stable. On physical exam, patient was stuporous with positive blinking reflexes. There was clinical evidence of volume contraction: skin turgor was lost and mucous membranes were dry.

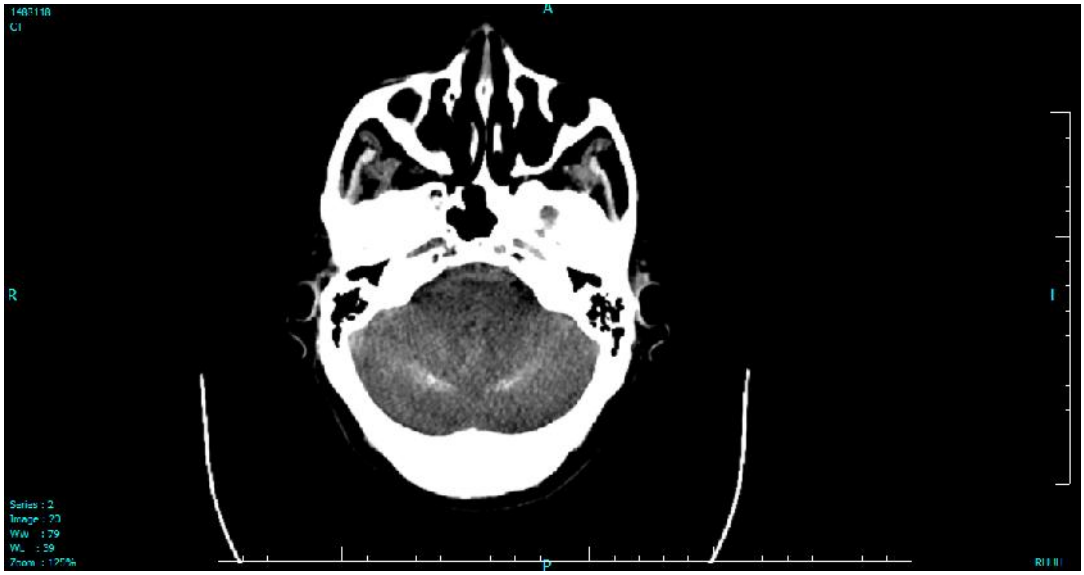

**Figure 1. Computed tomography scan of the brain showing bilateral cerebellar calcifications**

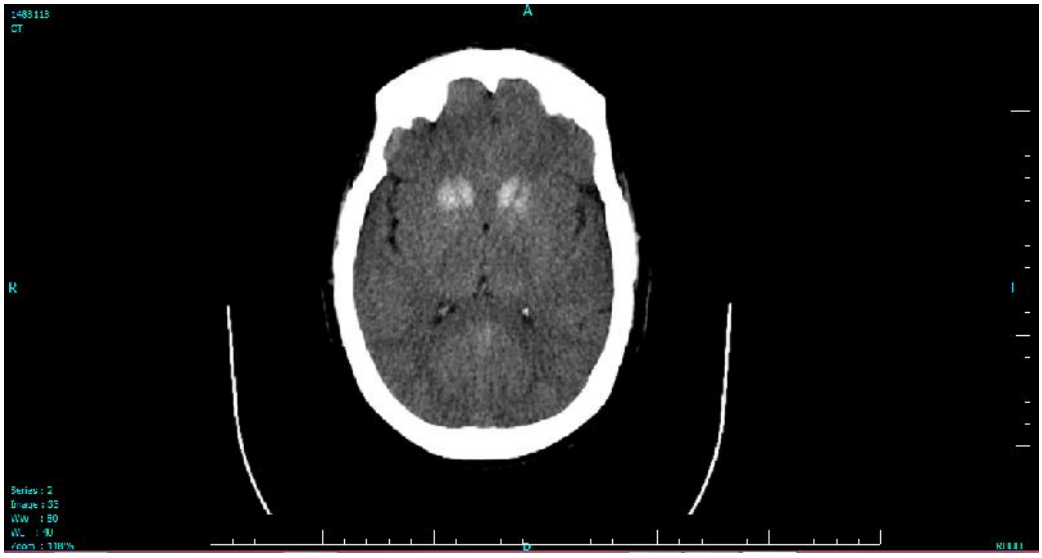

**Figure 2. Computed tomography scan of the brain showing bilateral basal ganglia calcifications**

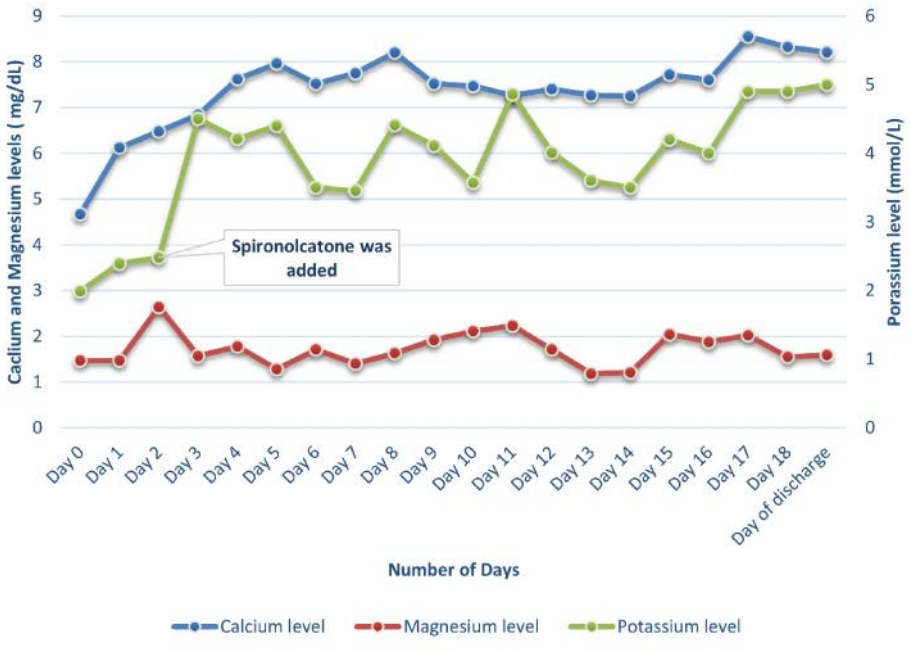


**Figure 3. Variation of calcium, magnesium and potassium levels during hospitalization**

She had diffuse hyporeflexia and rigidity. Chvostek and Trousseau signs were both positive. Occasionally, the patient had a staring look with myoclonic discharges occurring for ten to fifteen minutes which were suppressed with antiepileptic medications.

**Diagnostic testing:** Investigations were as follows: potassium level was 1.99 mmol/L (normal range 3.5-5.1 mmol/L), carbon dioxide level was 37 mmol/L (normal range 22-29 mmol/L), calcium level was 4.67 mg/dL (normal range 8.6-10 mg/dL), phosphorus level was 4.33 mg/dL (normal range 2.5-4.5 mg/dL) and magnesium level was 1.47 mg/dL (normal range 1.6-2.4 mg/dL). CT brain done showed bilateral basal ganglia calcification, more prominent in the caudate nucleus as well as bilateral cerebellar calcifications (Figures 1 and 2). Lumbar puncture was done to rule out meningitis given the fact that the patient had a lumboperitoneal shunt. Results of the latter were negative and diagnosis of meningitis was ruled out. Further workup of the patient's hypocalcemia came as follows: low PTH of 5 pg/mL (normal value 15-65 pg/mL), low 25-OH vitamin D level of 21 ng/mL (insufficiency = 30 ng/mL). Her TSH level was suppressed to 0.02 uIU/mL (normal range 0.27-4.2 uIU/mL) with low FT3 level of 1.65 pg/mL (normal range 2-4.43 pg/mL) and normal FT4 level of 1.69 ng/mL (normal range 0.93-1.7 ng/mL) which were attributed to non-thyroidal illness.

**Therapeutic intervention:** The patient was started on intravenous calcium gluconate 10% ampoule three times daily, potassium chloride 60 meq per 24h and magnesium sulfate 20% ampoule three times daily. Secondary to patient's altered mentation and inability to swallow, she was given intravenous alfacalcidiol 0.1 mcg three times daily. A nasogastric tube was inserted and she was started simultaneously on calcium carbonate 600 mg 1 tab per nasogastric tube three times daily along with Vitamin D3 100000 IU once. With intravenous correction, patient's calcemia increased to 7.95 mg/dL and her magnesium level to 1.8 mg/dL. However, she had refractory hypokalemia despite correction with 80 meq/day of intravenous potassium chloride that necessitated spironolactone 50 mg per nasogastric tube once daily for it to increase to 4 mmol/L (figure 3). Once the patient's level of consciousness started improving, per os intake was resumed as well as per os medications. Intravenous alfacalcidiol was shifted to 0.1 mcg three times per os daily. Intravenous calcium gluconate, magnesium sulfate and potassium chloride were discontinued. Per os calcium carbonate 600 mg 2 tabs three times daily and spironolactone 25 mg once daily were continued and the patient was started on magnesium dehydrate 470 mg per os three times daily.

**Outcome and follow-up:** Patient's status significantly improved. She only complained of persistent stiffness in both lower limbs for which physiotherapy sessions were done. On discharge, her calcemia increased 8.21 mg/dL, potassium to 5 mmol/L, magnesium level to 1.59mg/dL and carbon dioxide decreased to 25.5 mmo/L and phosphorus to 3.45 mg/dL. The patient was advised to continue oral supplements and to follow up with laboratory tests on a monthly basis.

## DISCUSSION

The patient described above has primary hypoparathyroidism as evidenced by severe hypocalcemia with low intact PTH. She also has laboratory findings in favour of Bartter syndrome: borderline blood pressure, hypokalemia, metabolic alkalosis and hypomagnesemia. After ruling out post- surgical hypoparathyroidism and autoimmune causes, the most probable cause remains an activating mutation of the CaSR causing Bartter type V syndrome. The fact that the patient had basal ganglia calcifications implies she had chronic hypocalcemia with late occurrence of severe symptoms such as status epilepticus. CaSR is a 1,078 amino acid G-protein-coupled receptor which consists of an extracellular domain of 612 amino acids, seven transmembrane domains of 250 amino acids and an intracellular domain of 216 amino acids with extracellular ionized calcium being its endogenous ligand (Choi, 2015). It is highly expressed in the parathyroid gland where the parathyroid cells detect small changes in calcium concentration and modulate the secretion of PTH (Hebert, 1997). Moreover, the CaSR is also present in abundance in the kidney on the basolateral side of the cortical thick ascending limb of the loop of Henle (TALH) in rats. Calcium and magnesium in the TALH are reabsorbed by a paracellular pathway driven by a positive luminal potential; with potassium excretion through the renal outer medullary potassium (ROMK) channel being essential to the generation of this positive luminal voltage relative to the basolateral side. Once activated by a high extracellular concentration of calcium ions, the CaSR inhibits the ROMK channel in the apical membrane and the sodium potassium ATPase in the basolateral membrane of the TALH thus increasing urinary calcium and magnesium excretion (Chattopadhyay, 1996; Watanabe, 2002 Vezzoli *et al.,* 2006). Activating mutations in different domains of the CaSR lead to hyper- responsiveness to extracellular calcium, which causes hypocalcemia with hypercalciuria, a disorder called autosomal dominant hypocalcemia (ADH). Similar mutations may also cause a Bartter phenotype by inhibition of transporters in the TALH and these patients present with characteristic sets of metabolic abnormalities: hypokalemia, metabolic alkalosis, hyper-reninemic hyperaldosteronism, hypomagnesemia and hypocalcemia ( Chattopadhyay, 1996; Watanabe, 2002 Vezzoli *et al.,* 2006; Kurtz *et al.,* 1998).

Many cases of Bartter's syndrome type V have been reported in association with CaSR mutations. All affected patients had symptomatic hypocalcemia. However, the time of onset of symptoms and their severity as well as Bartter phenotype varied according to the type of mutation ( Yousefichijan, 2017). Of these, two siblings with *K29E* mutation, one patient with Y829C mutation and patients with *K47N* or *P221L* mutations presented with hypocalcemia and mild hypokalemia without alkalosis, hyperreninemia, and hyperaldosteronemia and in the former three cases, first occurrence of symptoms was in early adulthood (Choi *et al.,* 2015; Vezzoli *et al.,* 2006). Whereas in patients with *A843E* mutation, the features of Bartter syndrome and hypocalcemia developed soon after birth (Watanabe, 2002) and in *L125P*, *C131W* and *A843E* mutations, classical Bartter's phenotype with hypocalcemia and hypercalciuria were seen (Yousefichijan, 2017). This phenotypic variation depends on the extracellular calcium concentration at which the mutated CaSR developed half of its maximal activity (EC50). The lower the EC50, the higher is the activity of the CaSR. The *K29E* mutation was previously reported as one of the most activating mutations of the CaSR gene. While the EC50 was 1.45 mmol/L for the *K29E* mutation, it was 3.16 mmol/L for the CaSR of the wild-type and lower than 1.5 mmol/L in previously described Bartter type V patients bearing an *L125P*, *A843E* or *C131W* mutations

of the CaSR thus indicating that it is in fact the latter two mutations that are the most activating of the CaSR and therefore cause the most severe symptoms ( Choi *et al.*, 2015; Watanabe, 2002; Hu, 2004). Furthermore, in 2009, Chrispal et al reviewed a 39-year-old patient who developed Bartter syndrome type V secondary to short-term amikacin therapy. In this case, amikacin was thought to have triggered the CaSR in the distal tubule of the thick ascending loop of Henle. This phenomenon has also been described with gentamicin with recovery occurring 15 days after drug cessation (Chrispal, 2009). The fact that our patient presented at a relatively late age could be related to a not yet identified CaSR mutation or to the simple fact of poor follow up or absence of a stressor that would alter the patient's steady state. However, for financial reasons, gene sequencing could not be done. Molecular genetic studies are indicated to identify the primary genetic defect in this patient. Treatment of Bartter type V can be quite challenging. Attempts should be made to raise serum calcium levels only in symptomatic patients. This is due to the fact that raising serum calcium will further activate the CaSR in the loop of Henle which then leads to an even higher increase in urinary calcium excretion and therefore nephrocalcinosis and renal failure. For this to be avoided, it is important to maintain a serum calcium concentration just sufficient to alleviate symptoms (Burren *et al.*, 2005). An additional option is to add a thiazide diuretic to reduce hypercalciuria if present and raise serum calcium simultaneously ( Sato *et al.*, 2002).

**Conclusion**

Bartter type V is a rare disorder resulting from an activating mutation of the CaSR. It almost always presents in childhood or early adulthood; however, it is subject to phenotypic variation according to the type of mutation. Treatment can be challenging and is associated with a high potential for adverse effects.

**Patient consent:** Written informed consent has been obtained from the patient for publication of the submitted article and accompanying images.

**Declaration of interest:** The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

**Author contributions and acknowledgements**

Dr Salwa Nassif Azar : wrote this article; Dr Mohamad Souheil EL Rawas : patient's physician, revised critically this manuscript and gave final approval of the version; Dr Patrick CharbelSarkis: participated in drafting this manuscript; Dr Akram Salim Echtay: revised critically this manuscript and gave final approval.

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