Open Journal of
Clinical & Medical
Case Reports

Volume 6 (2020)
Issue 11

ISSN: 2379-1039

An unusual case of Barter syndrome and primary hyperparathyroidism

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Abstract

Barter Syndrome (BS) is a genetic disease inherited as an autosomal recessive trait (Bartter type 1 to 4) or dominant disease (Barter type 5). The disease is associated with hypokalemic metabolic alkalosis and variable levels of hypercalciuria. Hypercalcaemia due to hypocalciuria in such patients is exceedingly rare. A 27-year-old female diagnosed with Type III Barter syndrome since early childhood that was treated by treated with Aldactone and potassium supplementation. She presented with fatigue, loss of appetite, cramps and constipation. Her physical examination was normal. Laboratory workup revealed: Potassium = 3.7 mmol/L (r.v.3.5–5.1), and calcium = 2.65 mmol/L (r.v.2.15–2.50). Further investigation confirmed hypercalcaemia due to primary hyperparathyroidism (PTH = 21.1 pmol/L (r.v 0.50-6.89)) owing to a single parathyroid adenoma. Following parathyroidectomy, serum calcium normalized.

Keywords

Barter syndrome; hyperparathyroidism; hypercalcaemia; parathyroid adenoma; renal tubular disorders.

Introduction

Bartter syndrome, first described by Bartter and colleagues in 1962, [1] represents a renal tubular disorder characterized by hypokalemia, hypochloremia, metabolic alkalosis, with hyperreninemia and normal blood pressure [2]. In Barter syndrome the kidneys is unable to regulate the composition and volume of body fluids. The normal function of loop of Henle, which reabsorbs a consistent fraction (about 30%) of fluids and electrolytes produced by glomerular blood filtration, is impaired. Mutations of several genes may result in BS, which is a genetically heterogeneous disease [3-5]. Hypercalciuria is a common feature in BS, nevertheless, the total plasma calcium concentration has been reported to be normal [6-8]. Rarely hypercalcaemia can occur in the course of BS. Therefore, the association of hypercalcaemia with BS necessitates further investigation. Herein, we describe a rare case of BS associated with mild hypercalcaemia

that was proved to be result of presence of Primary H yperparathyroidism (PHPT).

Case Report

A 27-year-old Caucasian woman diagnosed with Barter syndrome type III since early childhood. It was controlled medically by Mg oxide (400 mg, once daily), slow K (40 mmol 5 times /d) and Aldactone (25 mg once daily). She presented to the OPD in 2018 due to fatigue, loss of appetite, cramps and constipation. Her blood tests revealed a normal level of serum K, high serum Ca = 2.65 mmol/L (r.v.2.15–2.50). Physical examination was normal blood pressure 120/80 mm Hg, pulse rate 75 bpm, no stigmata of hypercortisolism and no focal neurological signs. The urine analysis shows normal calcium level. The patient's laboratory findings are shown in Table 1.

Further investigation revealed elevated parathormone hormone (PTH = 21.1 pmol/L (r.v 0.50-6.89)). Neck ultrasonography was request to assess parathyroid gland abnormalities (Figure 1). It revealed a hypervascular, hypoechoic nodule with 20 × 9 × 15 mm at the inferior pole of right thyroid lobe and medial to the right carotid artery, suggestive of parathyroid adenoma. To confirm our clinical suspicion of parathyroid adenoma Technetium 99m-MIBI-SPECT (Figure 2) that showed hypodense lesion posterior and inferior to the right thyroid lobe between the esophagus and the right carotid artery with tracer uptake on the right side, consistent with diagnosis of parathyroid adenoma.

She was treated by an inferior right parathyroidectomy. Post-operative histopathological analysis revealed parathyroid adenoma. Serum Ca and PTH normalized after surgery. Medical treatment prior to the surgery was maintained and during 6 months, follow-up normocalcaemia persists. The patient's post-operative laboratory findings are shown in Table 2.

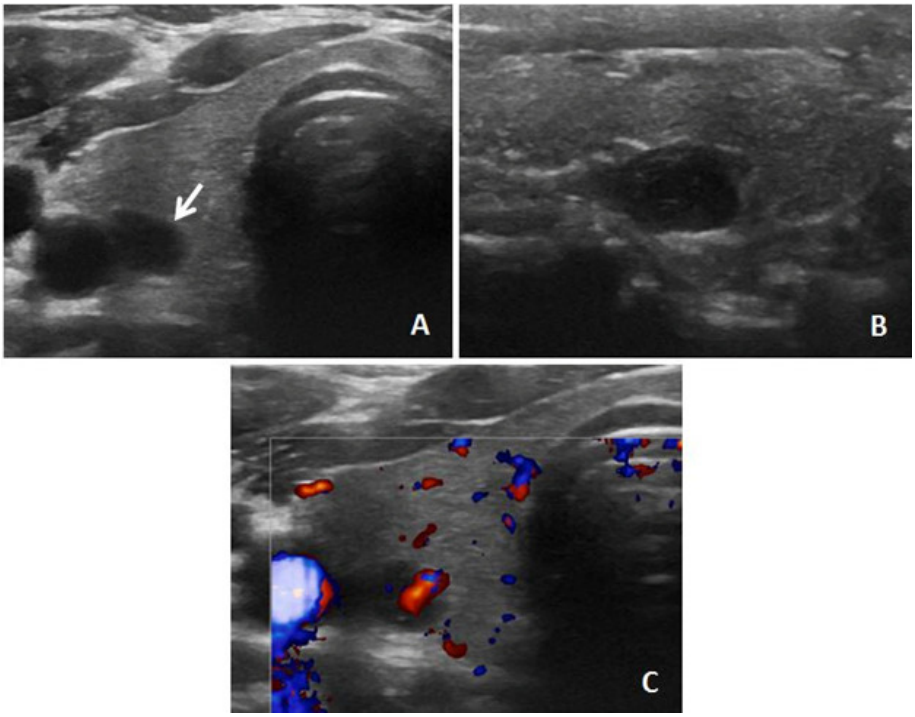

Figure 1: (A&B): B-mode ultrasound images in transverse and longitudinal planes show hypoechoic lesion related to the inferior pole of the right thyroid lobe and medial to the right common carotid artery. **(C):** Color Doppler image demonstrates the high vascularity of the lesion.

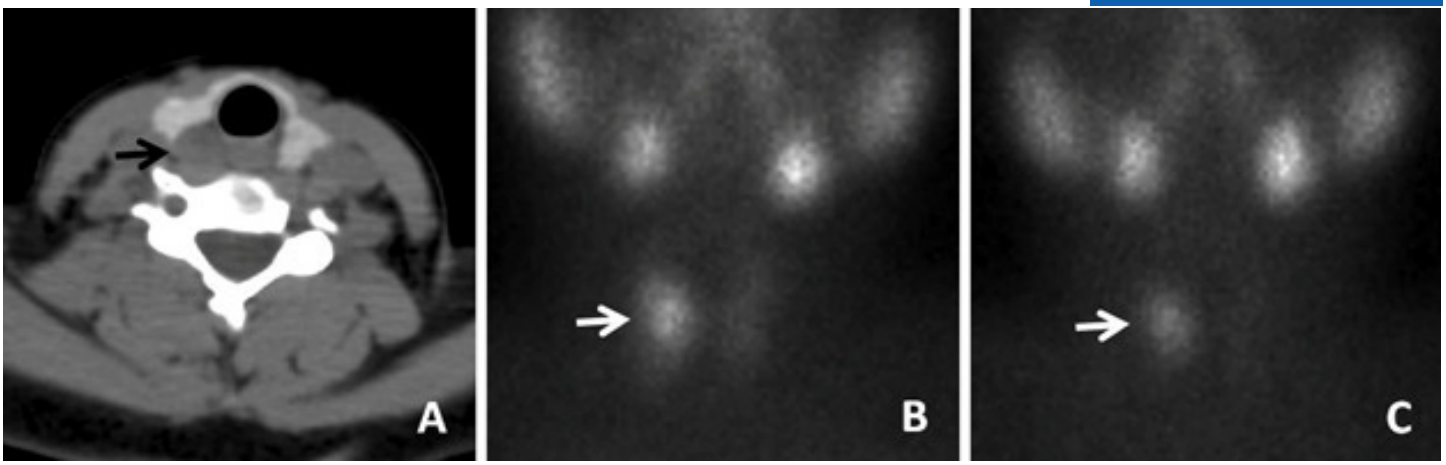

Figure 2: (A): Non enhanced axial CT scan through the thyroid gland shows hypodense lesion posterior to the thyroid lobe. **(B&C)**: early and late MIBI scan show high tracer uptake by right side neck lesion, consistent with parathyroid adenoma.

Table 1: Preoperative laboratory and urine analysis results.

Laboratory tests			
	Result	**Reference value**	**Unite**
PTH	21.1	0.50-6.89	pmol/L
Sodium	137	136-145	mmol/L
Potassium	3.7	3.5–5.1	mmol/L
Chloride	94.2	98-107	mmol/L
Calcium	2.65	2.15–2.50	mmol/L
Phosphorus	0.87	0.81-1.45	mmol/L
Magnesium	0.70	0.66-1.07	mmol/L
Total CO_2	29.0	22-29	mmol/L
Anion gap	13.8	8.0-16.0	
Blood urea	4.5	2.14-7.14	mmol/L
Serum creatinine	80	44-80	umol/L
Uric acid	298	142.8-339	umol/L
Glucose	5.7	4.11-5.89	mmol/L
Total protein	71.4	64-83	g/L
Albumin	38.9	35-52	g/L
Urine analysis			
	Result	**Reference value**	**Unite**
Urine calcium	2.04	0.20-7.5	mmol/L
Urine calcium 24 h	5.50	1.00-8.00	mmol/ 24 H
Urine volume	2700	400-2500	ml/24 h

Table 2: Post - operative laboratory and urine analysis results.

Laboratory tests			
	Result	**Reference value**	**Unite**
PTH	5.5	0.50-6.89	pmol/L
Sodium	139	136-145	mmol/L
Potassium	3.8	3.5–5.1	mmol/L
Chloride	93.8	98-107	mmol/L
Calcium	2.25	2.15–2.50	mmol/L
Phosphorus	0.85	0.81-1.45	mmol/L
Magnesium	0.78	0.66-1.07	mmol/L
Total CO_2	26.0	22-29	mmol/L
Anion gap	13.5	8.0-16.0	
Blood urea	4.4	2.14-7.14	mmol/L
Serum creatinine	80	44-80	umol/L
Uric acid	278	142.8-339	umol/L

Discussion

Type 3 BS is associated with mutation in CLCNKB gene, giving rise to a defective chloride channel Kb (ClC-Kb). Currently this type is called classic Bartter syndrome [6]. Type 3 Bartter syndrome patients have the mildest presentation, although CLCNKB is mutated, CLCNKA chloride permeability is still preserved [8]. Plasma calcium level is normal in BS, with the exception of rare patients with a BS type 5 that results from autosomal dominant, L125P mutations of an extracellular basolateral CASR, giving rise to hypocalcemic hypercalciuria and suppressed parathyroid hormone activity, in addition to the usual biochemical profile of Barter syndrome [7-9].

Rodríguez-Soriano et al. [10] reported slight elevation in serum calcium level in BS with a normal GFR and PTH levels.

As in our case, Betinelli et al. [11] described slight increase serum PTH with subsequent hypercalcemia in a genotypically mixed cohort of BS patients when compared to age-matched controls. Furthermore Landau et al. [12] compared PTH level between patients with ROMK-deficient type II BS and Barttin deficient type IV BS and found out that PTH has significantly increased in type II in comparison to type IV BS which might be a result of severe long-standing hypercalciuria.

Rego et al. [13] reported a rare association between Gitelman syndrome (GS) and primary hyperparathyroidism caused by parathyroid adenoma. Gitelman syndrome was first described in 1966 in a family characterized by hypokalaemia, hypomagnesaemia and hypocalciuria in contrary to Barter syndrome [14]. Similar to Barter syndrome, GS is caused by the alteration of a carrier involved in sodium chloride (NaCl) reabsorption, however the GS transporter is located in the distal convoluted tubules [6].

The tubular defect found in Bartter syndrome simulate that of chronic ingestion of loop diuretics, while in Gitelman syndrome, it is the same as in chronic ingestion of thiazide diuretics [15].

Differentiation of PHPT from familial hypocalciuric hypercalcemia (FHH) is for great importance as the latter is a benign inherited condition that does not require parathyroidectomy, nor will it be cured by it. In most patients, FHH is caused by loss-of-function mutation in calcium-sensing receptor (CaSR) gene presented on long arm of chromosome 3 (over 85%) [16]. Diagnosis of FHH can be easy to make in asymptomatic hypercalcemic patient with family history of hypercalcemia, history of failed neck exploration, or normal serum PTH [17]. Differentiation between PHPT and FHH is more difficult in absence of family history of hypercalcemia , if PTH level is normal or if the Ca/Cr ratio is greater than 0.01 and less than 0.02. Besides, age at diagnosis of hypercalcemia and Family History (FH) are of significant importance. Detection of asymptomatic hypercalcemia before the age of 40 is in favor to the diagnosis of FHH. Moreover, obtaining serum calcium values from first-degree relatives with no FH could be helpful [18].

To the best of authors' knowledge, this is the first case report to describe the association between BS & hypercalcaemia as a result to primary hyperparathyroidism and parathyroid adenoma. In PHPT, hypercalcaemia results from improper hypersecretion of PTH from parathyroid gland. Parathormone hormone raises tubular renal reabsorption of calcium, stimulates release of skeletal calcium storage and upregulates 1α- hydroxylase leading to elevation in 1,25-(OH)2D3 production and bowel calcium absorption [13,19]. Our patient was managed successfully by parathyroidectomy and maintained on lifelong medical therapy to control Barter syndrome.

Conclusion

In conclusion, the presence of hypercalcemia in the course of BS could be a consequence to severe prolonged hypercalciuria as described in previous literature [11,12], however it requires further evaluation in order to exclude underlying PHPT.

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Manuscript Information: Received: January 28, 2020; Accepted: June 05, 2020; Published: June 30, 2020

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Citation: Fathallah A, Elmokadem AH, Ali H, Khudadah K, Hamdy N. An unusual case of Barter syndrome and primary hyperparathyroidism. Open J Clin Med Case Rep. 2020; 1674.