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Case Report

A Case of Familial Hypocalciuric Hypercalcemia

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Abstract

Background: *Primary hyperparathyroidism (PHPT) is a common endocrine disorder that is the leading benign cause of hypercalcemia. It may occur due to autonomous hypersecretion of parathyroid hormone (PTH), independently of serum calcium levels. Familial hypocalciuric hypercalcemia (FHH) is a group of autosomal dominant rare genetic diseases only affecting the regulation of calcium metabolism. It is usually caused by one of many heterozygous missense mutations in the calcium-sensing receptor (CaSR) gene, which could up-regulate the set point of parathyroid cells. When the CaSR receptor is inactivated, PTH is not suppressed despite relatively high calcium, which makes FHH similar to PHPT. We present a unique case of concomitant FHH and suspected parathyroid adenoma.*

Case summary: *A 10-year-old girl with symptomatic severe hypercalcemia, high PTH, and genetically diagnosed as FHH was referred to the department of otolaryngology-head and neck surgery due to surgical excision of suspected parathyroid adenoma. Her biochemical evaluation showed elevated serum calcium and PTH. The calcium–creatinine clearance ratio was >0.01 (0.16). Her parathyroid scintigraphy showed negative for parathyroid adenoma, but the ultrasonography of the neck revealed an enlarged right inferior parathyroid gland. She underwent surgical excision of both the right superior and inferior parathyroid glands. However, the patient's serum calcium and parathyroid hormone increased in the postoperative period, and her symptoms remained unchanged.*

Conclusion: *The correct diagnosis of the underlying cause of hypercalcemia is essential to ensure the proper treatment. Patients with FHH should avoid operative treatment, and PHPT should be differentiated to determine whether surgery should include parathyroidectomy with the removal of suspected parathyroid adenoma.*

Keywords: *Primary hyperparathyroidism, Familial hypocalciuric hypercalcemia, Parathyroid adenoma.*

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Introduction:

Primary hyperparathyroidism (PHPT) is a common endocrine disorder that is the leading benign cause of hypercalcemia. It may occur due to autonomous hypersecretion of parathyroid hormone (PTH), regardless of serum calcium levels. Parathyroid adenoma(s) and parathyroid hyperplasia are the leading causes of PHPT[1]. Familiar forms of PHPT (FPHPT) represent less than 5% of total PHPT cases, including familial hypocalciuric hypercalcemia (FHH) and multiple endocrine neoplasia types 1 and 2A (MEN1 and MEN2A)[2]. In 1972, Foley and his associates first described familial benign hypercalcemia as a group of autosomal dominant rare genetic diseases only affecting the regulation of calcium metabolism[3]. However, for the same disorder, the term "familial hypocalciuric hypercalcemia" (FHH) was first used by Marx and his co-workers in 1977[4]. Type 1 FHH is the commonest variant representing 65% of the cases, first reported by Pollack et al. in 1993[5,6]. It is usually caused by one of many heterozygous missense mutations in the calcium-sensing receptor (CaSR) gene, which could up-regulate the set point of parathyroid cells. When the CaSR receptor is inactivated, PTH is not suppressed despite relatively high calcium, which makes FHH similar to PHPT[7]. Since then, other pathogenic variants in the G-protein subunit á11 (GNA11) and adaptor-related protein complex 2, sigma 1 subunit (AP2S1) have been introduced in a clinical practice known as type 2 and type 3, respectively[8]. The pathogenic variants lead to lifelong hypercalcemia, a generally benign disorder that does not require medical treatment or surgery. Most patients with FHH are asymptomatic, but chondrocalcinosis, acute pancreatitis, or even nephrolithiasis have occasionally been observed[9-11].

Case Report

A10 years old girl referred from department of Paediatrics to department of otolaryngology-head and neck surgery, Bangabandhu Sheikh Mujib Medical University as a diagnosed case of familial hypocalciuric hypercalcaemia (FHH). Patient had history of intermittent abdominal pain and vomiting and had got several time hospital admissions as a case of chronic calcific pancreatitis. She underwent two times ERCP for removal of pancreatic duct calculi and placement of pancreatic duct stenting. She received monthly bisphosphonates according to serum calcium report. Her genetic study revealed mutation in CaSR gene which is likely compound heterozygous missense variants in exon 3 and exon 4 (Table 1).Her elder sister is also diagnosed as a case of familiar hypocalciurichypercalcaemia but asymptomatic. Other family members are also asymptomatic.

Investigations

Blood investigations revealed severe hypercalcaemia (serum calcium of 17.5 mg/dl) with a PTH of222.1 pg/ml at time of presentations (Table 2). The calculated CCCR was 0.16 (Table 3). A 24 h urine metanephrines assay was normal.

Table I : *Result of genetic analysis.*

Gene (Transcripts) #	Location	Variant	Zygosity	Disease	Classification
CaSR (+)	Exon 3	c.217G>C	Heterozygous	severe	Likely
(ENST0000		(p.Ala73Pro)		Hyperparathyroidism	Pathogenic
0498619.4)	Exon 4	c.911T>C	Heterozygous		Uncertain
		(p.Leu304Pro)			Significance

Table II : *Results of biochemical blood tests.*

Blood parameters	Normal ranges	Case
Sodium (mmol/L)	136-145	134
Potassium (mmol/L)	3.5-5.5	3.6
Chloride (mmol/L)	98-107	104
T-CO_2 (mmol/L)	20-31	23.2
Calcium (mg/dl)	8.3-10.6	17.5
PTH (pg/ml)	18.5-88	222.1
TSH (mU/L)	0.3-5	2.1
25-hydroxy vitamin D (nmol/L)	>30	16
Uric Acid (mg/dl)	3.1-7.8	4.4
Albumin (gm/L)	32-48	45
Alkaline Phosphatase (U/L)	46-116	336
AST (SGOT) (U/L)	<34	35
ALT (SGPT) (U/L)	10-49	31
Creatinine (mg/dl)	0.5-1.1	0.32

PTH: parathyroid hormone; TSH: thyroid stimulating hormone; AST: Aspartate transaminase; ALT: alanine transaminase.

Table III : *Results of urine analysis.*

Urinary parameters	Normal ranges	Case
Calcium (mg/24h)	100-300	89
Creatinine (mg/dl)	20-275	39.62
Calcium creatinine clearance ratio (%)	>0.01	0.16

Preoperative workup with an ultrasound neck revealed an enlarged (11×6mm) right inferior parathyroid gland (Figure 1) suspected for parathyroid adenoma but a sestamibi scan demonstrated no focal area of increased radiotracer concentration in and around thyroid gland or mediastinal region.

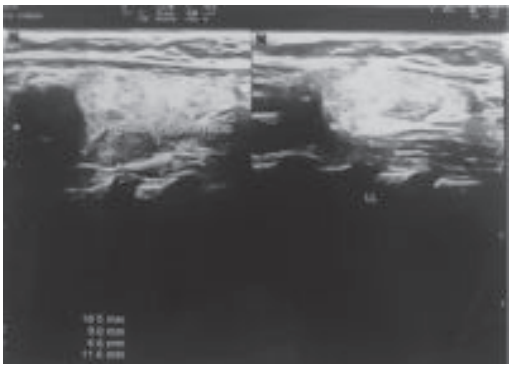

Fig.-1: *USG showing suspected right inferior parathyroid adenoma.*

Intervention

In department of otolaryngology-head and neck surgery, she underwent surgical excision of both right superior and inferior parathyroid gland.

Outcome and follow-up

An unusual association of serum parathyroid hormone and serum calcium levels (Table IV) were shown during follow-up period.The patient remained symptomatic with both raised serum calcium level and serum parathyroid hormone level.

Table IV : *Pre, per and post operative serum parathyroid hormone and serum calcium levels.*

		S. PTH	S. Calcium
Preoperative		222.1 pg/ml	17.5 mg/dl
Per-operative	Pre incision	409.8 pg/ml	
	Just after excision of right inferior parathyroid gland	322.6 pg/ml	
	10 minutes after excision of right inferior parathyroid gland	304.6 pg/ml	
	10 minutes after excision of right superior parathyroid gland	iPTH 146.6 ng/ml	
Post-operative	2nd post-operative day	553.8 pg/ml	13.8 mg/dl
	23rd post-operative day	153.6 pg/ml	16.1 mg/dl

Discussion:

This case is an example of primary hyperparathyroidism secondary to suspected parathyroid adenoma in a patient with concomitant type 1 FHH. A small number of similar cases have been reported[12-16]. In 2002, the first case of a parathyroid adenoma with FHH was reported. A 45 year old woman had a history of severe symptomatic hypercalcemia, elevated PTH levels, hypocalciuria and a family history of hypercalcemia. A parathyroid adenoma was identified by scintigraphy and the genetic analysis for FHH was positive. The parathyroid adenoma was surgically removed, significantly improving symptoms and serum calcium levels[12]. The other reported cases occurred in patients with FHH who developed worsening hypercalcaemia on follow-up with corresponding elevations in PTH levels. After locating parathyroid adenomas with scintigraphy, a parathyroid surgery was performed and postoperatively, their serum calcium levels dropped to just above the normal range[13-16].

It can be challenging to differentiate between primary hyperparathyroidism and FHH as many overlapping clinical features exist. Although a raised serum PTH in the setting of hypercalcaemia suggests a diagnosis of primary hyperparathyroidism, PTH may also be elevated in FHH. In 2008, a published cross-sectional study reported the prevalence of elevated PTH levels in patients with FHH to be 23%[17].

According to the consensus guidelines, performing 24 h urinary calcium is part of the initial evaluation of patients with hypercalcaemia[18]. It showed the characteristic hypocalciuria and urinary calcium/creatinine clearance ratio <0.01, which prompted genetic testing[19,20]. Although the urinary calcium/creatinine clearance ratio is the consensus biochemical test to differentiate between FHH and primary hyperparathyroidism, 15–20% of patients with FHH exhibit borderline renal clearance and have a urinary calcium creatinine clearance ratio >0.01[21]. This case showed a similar urinary calcium creatinine clearance ratio >0.01 (0.16) and genetic analysis revealed the compound heterozygous missense mutation in CaSR, which indicate type 1 FHH.

Although surgery is not indicated in managing FHH, these case reports of patients with a combination of FHH and suspected parathyroid adenomas suggest a beneficial effect from surgical resection of the adenoma with improvement in symptoms and biochemical markers following surgery[12-16]. However, in contrast, our patient's serum calcium and parathyroid hormone increased in the postoperative period, and her symptoms remained unchanged, which was unclear and unusual. It is also unclear whether the development of suspected parathyroid adenomas in patients with FHH is coincidental or not. Although CaSR expression is decreased in parathyroid adenomas[22], previous studies have shown no mutations in the CaSR gene in parathyroid adenomas. Therefore, a causal link between the two conditions has not yet been established[23].

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