Scintigraphy Negative Ultrasound Positive Parathyroid Adenoma in Familial Hypocalciuric Hypercalcaemia

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ABSTRACT

Familial hypocalciuric hypercalcemia (FHH) is a rare, lifelong, benign condition with an autosomal dominant pattern of inheritance. FHH is clinically distinguished by mild to moderate PTH-dependent hypercalcemia and normal to significantly reduced urinary calcium excretion despite elevated serum calcium. FHH is usually caused by a heterozygous loss-of-function mutation in the calcium-sensing receptor gene (CaSR). It should be differentiated from primary hyperparathyroidism (PHPT). The reported case of a 10-year-old girl presented with symptomatic hypercalcemia, elevated intact parathyroid hormone, and a vitamin D deficiency. 99mTc-Sestamibi scan failed to detect any abnormalities, but high-resolution ultrasound (HRUS) of the neck revealed a right inferior parathyroid adenoma, which was excised with a focused parathyroidectomy. Although the patient's calcium and iPTH levels normalized initially, they started rising within a few days.

Keywords: Hypercalcemia, Familial hypocalciuric hypocalcemia, Primary hyperparathyroidism, Parathyroid adenoma, Parathyroid hormone.

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INTRODUCTION

Familial hypocalciuric hypercalcemia (FHH) is a rare, lifelong, benign condition usually caused by one of several heterozygous, inactivating mutations in the calcium sensing receptor (CaSR) gene. The common mutation loci associated with FHH occur on chromosomes 3 and 19 (19p13.3 and 19q13) (1). The CaSR is expressed in tissues like the parathyroid, thyroid, kidney, gut, pancreas, and bone. The CaSR mutation in FHH results in reduced sensitivity of CaSR to circulating calcium. Therefore, a normal level of calcium is perceived as low by the parathyroid glands, and parathyroid hormone (PTH) is released to increase the calcium concentration. The decreased receptor sensitivity in the distal nephron of the kidney results in hypocalciuria. These effects ultimately lead to a biochemical picture of compensatory hypercalcemia, an elevated or inappropriately normal parathyroid hormone level, and hypocalciuria in FHH (2). The inheritance of FHH is autosomal dominant. FFH was first reported in 1972 by Foley et al. (3, 4). However, the term "familial hypocalciuric hypercalcemia" (FHH) was first used by Marx and his co-workers in 1977 (4). Most patients with FHH are asymptomatic; about 2% of patients may complain of weakness, fatigue, polydipsia, psychiatric disorders, chondrocalcinosis, pancreatitis, or even nephrolithiasis, which have occasionally been observed (2). Primary hyperparathyroidism (PHPT) is a common endocrine disorder that is the leading cause of hypercalcemia. It may occur due to autonomous hypersecretion of parathyroid hormone (PTH), regardless of serum calcium levels. Parathyroid adenoma and parathyroid hyperplasia are the most common causes of PHPT. PTH is not suppressed despite relatively high calcium, which makes FHH similar to PHPT (3). It has clinical significance to differentiate FHH from primary hyperparathyroidism, as this could avoid unnecessary investigations and procedures.

CASE REPORT

A 10-year-old girl was requested a high-resolution ultrasonography of the neck and parathyroid scintigraphy

and referred to National Institute of Nuclear Medicine & Allied Sciences (NINMAS). She was previously diagnosed as having FHH. The patient had a history of symptomatic hypercalcemia, like intermittent abdominal pain and vomiting, and had been hospitalized several times for chronic calcific pancreatitis. She underwent two ERCPs for the removal of pancreatic duct calculi and the placement of pancreatic duct stenting. According to her serum calcium report, she was given bisphosphonates on a monthly basis. Her genetic study revealed a mutation in the CaSR gene, which is likely compound heterozygous missense variants in exon 3 and exon 4 (Table 1), consistent with FHH type 1. Her elder sister was diagnosed with familial hypocalciuric hypercalcemia as well, but she was asymptomatic.

Investigations

Blood investigations revealed severe hypercalcaemia (serum calcium of 17.5 mg/dl) with an elevated level of PTH of 222.1 pg/ml at time of presentations (Table 2). The calculated CCCR was 0.16 (Table 3).

Table 1: Result of genetic analysis.

Gene (Transcrips) #	Location	Variant	Zygosity	Disease	Classification
CaSR (+) (ENST00000498619.4)	Exon 3	c.217G>C **(p.Ala73Pro)**	Heterozygos	severe hyperparathyroidism	Likely Pathogenic
	Exon 4	c.911T>C **(p.Leu304Pro)**	Heterozygos		Uncertain Significance

HRUS of neck (Figure 1) revealed a small hypoechoic area near lower pole of right thyroid lobe measuring about (11.6×6.6mm) suspicion for enlarged right inferior parathyroid gland or parathyroid adenoma.

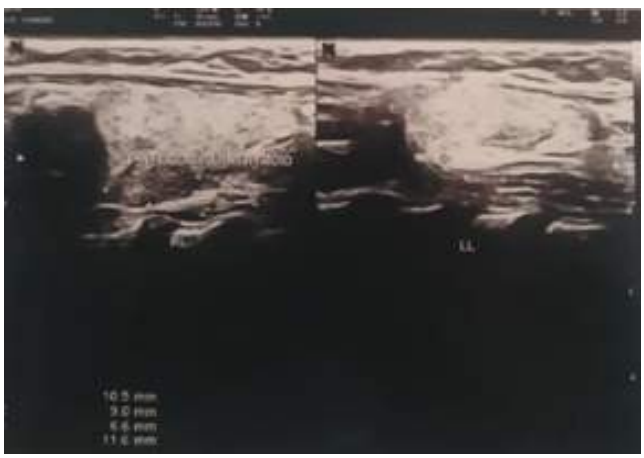

Figure 1: HRUS of neck image showing a small hypoechoic area near lower pole of right thyroid lobe suspicious of right inferior parathyroid adenoma.

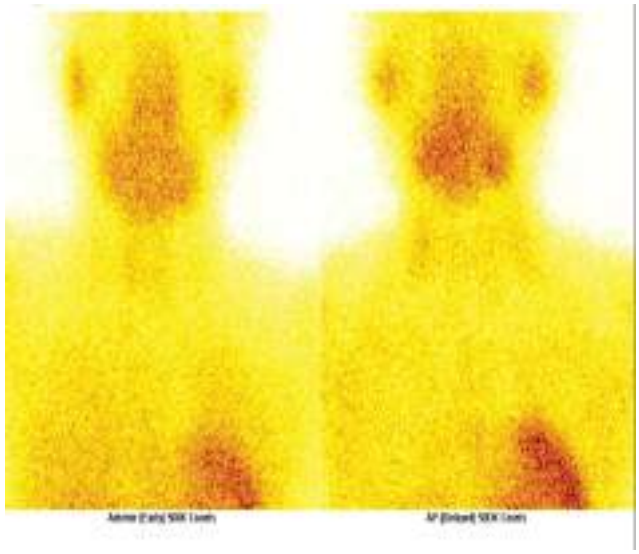

Figure 2: Early static image of 99mTc- Sestamibi scan showing normal sized thyroid gland with homogenous but diffusely decreased radiotracer concentration. Delayed static image shows complete washout of tracer from the thyroid gland with no focal area of increased radiotracer concentration in and around the thyroid gland or mediastinal region.

Static image (Figure 2) of 99mTc-Sestamibi scan could not detect any parathyroid adenoma in and around the thyroid gland or mediastinal region. SPECT image of 99mTc-sestamibi parathyroid scan also failed to determine any parathyroid adenoma.

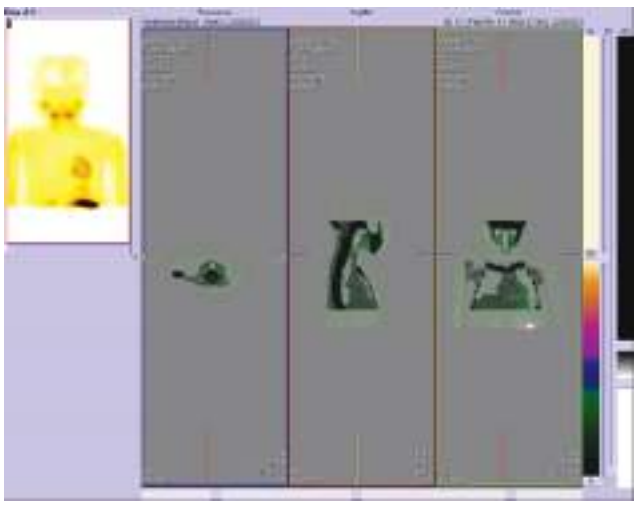

Figure 3: SPECT image of parathyroid scan demonstrated no focal area of increased radiotracer concentration in and around thyroid gland or mediastinal region in transaxial, coronal and sagittal section-which is negative for parathyroid hyperplasia or adenoma.

Table 2: Results of biochemical blood tests showing hypercalcemia and hyperparathyroidism, reduced vitamin D level. Electrolyte level, serum TSH, uric acid, albumin, SGPT, SGOT and creatinine level are within normal limit.

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 3: Results of urine analysis shows calcium creatinine ratio 0.16 which signifies need for genetic testing.

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

Intervention

Patient underwent surgical excision of both right superior and inferior parathyroid glands in the department of otolaryngology-head and neck surgery.

Outcome and follow-up

During the follow up period, there was an unusual association of serum PTH and serum calcium levels (Table 4) and the patient remained symptomatic with raised levels of both serum calcium and serum PTH.

Table 4: Serum parathyroid hormone (PTH) showing elevated in pre-operative period which started to reduce just after surgery but again elevated within 2nd post-operative day. On 23rd post- operative day it still remained high. Serum calcium level was elevated in pre-operative period, mildly reduced in 2nd post-operative day which was still high and still remained high within 23rd post-operative day.

Procedural timings	Procedure	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	
Postoperative	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

Although the clinical presentations and biochemical findings may overlap in PHPT and FHH, these two entities must be distinguished because of the drastic differences in treatment. Surgical removal of the parathyroid gland is recommended in PHPT, where no improvement is seen in patients with FHH (5). Calcimimetics are allosteric modulators of CaSR that aid the mutant receptor in becoming more sensitive to serum calcium levels. This increased sensitivity results in a reduction of PTH production and a normalization of serum calcium levels. Cinacalcet is currently the only drug in this class approved for human use and is currently indicated for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease and for the treatment of hypercalcemia in patients with FHH (6).

A cross-sectional study that was published in 2008 revealed that 23% of patients with FHH had increased PTH levels (7). When parathyroid glands were removed from FHH patients, histopathological investigations revealed glandular enlargement, most frequently mild parathyroid hyperplasia, but no evidence of adenoma development. One theory is that the CaSR gene's decreased activity causes fewer cell surface receptors, which stimulates the parathyroid cells' excessive growth (8).

In this reported case, it may be questioned whether the presence of FHH and a potential parathyroid adenoma is merely a coincidence or if the adenoma results from a secondary CaSR mutation. Marx SJ et al. demonstrated that PHPT and FHH should co-occur in 1 in 10 million people by chance because they are found in 1 in 1,000 and 1 in 10,000 population respectively, making the combination an extremely rare but probable. Based on a mutation in the cytoplasmic tail of CaSR, single or multiple parathyroid adenomas have recently been described in several family members with apparent FHH (8, 9). Only a few reported cases are comparable with the clinical scenario of this 10-year-old girl. Currently, genetic testing is the most reliable method of research (8).

Forde HE et al. reported a case of severe symptomatic hypercalcemia, elevated PTH levels, hypocalciuria, and a family history of hypercalcemia in a 45-year-old woman. Scintigraphy revealed a parathyroid adenoma, and positive result for FHH in genetic analysis. After the parathyroid adenoma was surgically removed, symptoms and serum calcium levels significantly improved (7). Whereas, serum calcium and PTH levels reduced following parathyroidectomy, but started rising within second post-operative day and returned back to the preoperative elevated level in this young girl. Therefore, removal of parathyroid glands was not effective in this case.

The initial evaluation of patients with hypercalcaemia, according to consensus guidelines, includes a 24-hour urinary calcium test (13). It prompted genetic testing because it displayed the typical hypocalciuria and urinary calcium/creatinine clearance ratio of 0.01. Although the urinary calcium/creatinine clearance ratio is the widely accepted biochemical test to distinguish between primary hyperparathyroidism and FHH, 15-20% of FHH patients have borderline renal clearance and a urinary calcium/creatinine clearance ratio that is greater than 0.01 (7, 10,14). Similar urinary calcium creatinine clearance ratio values were observed in this case (>0.01 [0.16]), and genetic testing revealed a compound heterozygous missense mutation in CASR, which denotes type 1 FHH. However, type 1 FHH is the commonest variant representing 65% of the cases, first reported by Pollack et al. in 1993 (11,12).

Although a suspected adenoma was found in the HRUS of the neck, a false negative parathyroid scan can be explained by facts like a very small adenoma, multiple tiny adenomas rather than a single adenoma, cystic changes in adenoma, and an adenoma not rich in oxyphil cells (15). Although surgery is not indicated in managing FHH, the above-mentioned case reports of patients with a combination of FHH and suspected parathyroid adenomas detected by HRUS of neck suggest a beneficial effect from surgical resection of the adenoma, with improvement in symptoms and biochemical markers following surgery in this patient. That's why parathyroidectomy was done in our case, and after surgery, the histopathology report of the resected specimen confirmed parathyroid tissue. In our case, the patient's serum calcium and parathyroid hormone were elevated in the postoperative period, and her symptoms remained unchanged in the follow-up period, which suggests parathyroid hyperplasia was secondary to FHH.

CONCLUSION

The correct diagnosis of the underlying cause of hypercalcemia is essential to ensure proper treatment. Reported patient's symptoms did not change over the follow-up period despite elevated levels of PTH and serum calcium in the postoperative period, suggesting that parathyroid hyperplasia was a result of FHH. 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 adenomas. On the other hand, symptomatic treatment should be given to patients with FHH.

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