Case Report

Retrospectively diagnosed familial hypocalciuric hypercalcaemia following total parathyroidectomy in an asymptomatic patient

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Abstract

Background

Familial hypocalciuric hypercalcemia (FHH) is a rare, benign condition that shares characteristics with primary hyperparathyroidism (PHPT), a more sinister condition that requires surgical intervention. This case report demonstrates misdiagnosis of FHH and highlights important learning points to prevent this in the future.

Case Presentation

Hypercalcaemia was incidentally discovered in a 21-year-old patient who had no symptoms of hypercalcaemia and no significant family history. Clinical examination was normal. Biochemical investigations revealed hypercalcaemia of 2.84mmol/L (2.15 – 2.50mmol/L) and hypophosphataemia of 0.71mmol/L (0.78 – 1.42mmol/L). Parathyroid hormone (PTH) concentration was mildly and inappropriately elevated (10.3pmol/L [2.0 – 8.5pmol/L]) triggering a suspicion of PTH-mediated hypercalcaemia. Parathyroid scintigraphy reported an ill-defined area of focal uptake above the left thyroid lobe. Fractional excretion of calcium estimations on 24hour urine collections were borderline (0.01) for FHH on multiple occasions however, further investigations to exclude FHH were not performed before a diagnosis of primary hyperparathyroidism was made, and a total parathyroidectomy performed. Several months post-operatively, the patient still demonstrated persistent hypercalcaemia. Her siblings had since been diagnosed with FHH. The patient was then retrospectively diagnosed with FHH. Genetic testing for FHH is not available in South Africa which limited the opportunity to confirm the diagnosis.

Conclusions

This case report provides a classical presentation of the rare, benign disorder of FHH. It highlights the negative outcomes that may result from misdiagnosis of this condition as PHPT. Biochemical investigations play an integral role in differentiating these conditions. Effective clinician-laboratory communication is crucial for optimal patient outcomes.

Introduction

Familial hypocalciuric hypercalcaemia (FHH) is a rare autosomal dominant condition caused by inactivating mutations in the calcium-sensing receptor (CaSR) gene.

FHH is characterised by lifelong hypercalcaemia which confers minimal, if any, morbidity [1]. Parathyroid hormone (PTH) concentrations may be normal or mildly elevated. Primary hyperparathyroidism (PHPT) is a relatively common endocrine disorder characterised by excess production of PTH and is associated with significant renal and skeletal complications over time [2]. While FHH shares features with PHPT, it is distinguished by demonstrating relative hypocalciuria for the degree of hypercalcaemia present. Family history, early age of onset and the lack of symptoms noted in FHH assists in differentiating it from PHPT, a distinction that significantly impacts appropriate management of the patient given that PHPT is treated surgically while FHH does not require treatment [3].

Case presentation

The patient is a 21-year-old female with no known co-morbid illnesses. She was incidentally found to be hypercalcaemic during baseline investigations performed for an elective procedure. No polyuria, constipation, abdominal or bone pain or any other symptoms of hypercalcaemia were reported. She had no previous history of renal calculi and no significant family history was noted. Clinical examination was normal.

Table 1: Blood investigation results.

Analyte	Result	Reference Interval
Urea	4.5mmol/L	2.1 – 7.1
Creatinine	88umol/L	49 – 90
Calcium	2.84mmol/L	2.15 – 2.50
Magnesium	0.98mmol/L	0.63 – 1.05
Phosphate	0.71mmol/L	0.78 – 1.42
Albumin	50g/L	35 – 52
PTH	10.3pmol/L	2.0 – 8.5
25-OH Vitamin D	43.80nmol/L	< 50.00 - Deficient

Laboratory investigations

Biochemical investigations revealed a hypercalcaemia of 2.84mmol/L (2.15 – 2.50mmol/L) and a hypophosphataemia of 0.71mmol/L (0.78 – 1.42mmol/L). PTH concentrations were mildly and inappropriately elevated at 10.3pmol/L (2.0 – 8.5pmol/L) leading clinicians to suspect a PTH-mediated hypercalcaemia. Vitamin D toxicity was ruled out with 25-OH Vitamin D concentrations which rather demonstrated a deficiency. Renal function was intact. Due to the young age of the patient and lack of symptoms, FHH was appropriately investigated for with the measurement of a urinary calcium: urinary creatinine clearance ratio (fractional excretion of calcium) on 24hour urine collections. This test was performed twice and on both occasions the clearance was borderline at 0.01. A fractional excretion of calcium <0.01 is indicative of FHH and >0.02 is suggestive of PHPT [4]. Parathyroid scintigraphy reported an ill-defined area of focal uptake above the left thyroid lobe. Skeletal survey and renal ultrasound confirmed the absence of skeletal abnormalities and renal calculi.

Table 2: Urine investigation results.

Test	Result	Reference Interval / Clinical Decision Limit
Urine Creatinine	2.7mmol/L	
Urine Calcium	0.99mmol/L	
Urine calcium: creatinine	0.37mmol/mmol creat	0.02 – 0.93
24-hour Urinary Calcium Excretion	0.01	< 0.01 – FHH > 0.02 - PHPT

Differential Diagnosis

A diagnosis of PHPT was made likely secondary to parathyroid hyperplasia or a parathyroid adenoma. This was based on the elevated PTH concentration and scintigraphy results.While molecular testing for CaSR gene mutations is not available in South Africa, FHH had not been excluded in this patient given the borderline calcium clearance ratio and clinical presentation. Testing of direct family members (parents and siblings) could have occurred to screen for asymptomatic hypercalcaemia with hypocalciuria. The patient underwent a total parathyroidectomy and all four glands demonstrated mild hyperplasia but no evidence of adenoma. Mild parathyroid hyperplasia is a feature in keeping with FHH [5]. The patient developed a mild hypocalcaemia post operatively but hungry bone syndrome, which is a relatively common post-operative complication of PHPT [4], was not observed. Several months post-operatively the patient was noted to have persistent hypercalcaemia which is a strong indicator of FHH rather than PHPT [6]. By this stage, the patient's siblings had been screened for FHH and three of the five siblings were found to have asymptomatic hypercalcaemia and 24-hour urine calcium clearance ratios <0.01 which confirmed the diagnosis of FHH in these siblings. A retrospective diagnosis of FHH was made in this patient. The patient and her siblings with FHH are reviewed annually and have been hypercalcaemic but asymptomatic to date.

Discussion

This case report highlights the role of the clinical laboratory in differentiating between two distinct conditions that share common features but are managed very differently – FHH and PHPT. It also demonstrates how lack of inadequate understanding of the pathophysiology of disease and its affect on biochemical findings may lead to misdiagnosis resulting in poorer patient outcomes. The raised PTH in the context of hypercalcaemia lead to a diagnosis of PHPT. However, consideration of the holistic picture, including pertinent history such as the age of the patient and lack of symptoms, and the borderline fractional excretion of calcium would have demonstrated the importance of excluding FHH in this patient, preventing an unnecessary surgical procedure. Consultation with the chemistry laboratory regarding further investigations to reach a definitive diagnosis may have been invaluable in this case.

Familial hypocalciuric hypercalcaemia (FHH) is a rare condition inherited in an autosomal dominant pattern equally distributed between the sexes. It's true prevalence is not known due to its subclinical nature in many cases [1]. It occurs as a result of mutations in the calcium-sensing receptor gene (CaSR) that lead to decreased receptor activity. The loss of function mutations in the CaSR gene in the parathyroid gland increases the set point for calcium sensing. It makes the parathyroid glands less sensitive to calcium, and a higher than normal serum calcium level is required to reduce PTH release. In the kidney, this defect leads to an increase in tubular calcium and magnesium reabsorption resulting in hypercalcemia, hypercalcaemia, and frequently high normal levels of serum magnesium [7]. Patients with FHH display higher levels of plasma PTH and it takes a higher level of plasma calcium to suppress PTH secretion.

Individuals with FHH will demonstrate lifelong hypercalcaemia, typically below 3.0mmol/l [5], as is seen in this patient with an inappropriately low urinary calcium excretion. Serum phosphate levels are often reduced, intact PTH levels are typically inappropriately normal in 80% of patients and mildly elevated in the remainder, and mild hypermagnesaemia may be present [6].

PHPT is characterised by excess PTH production by one or more of the parathyroid glands which can lead to significant skeletal, renal, abdominal, and neurological symptoms related to the resultant hypercalcaemia. PTH levels are often frankly elevated but may be within normal ranges in some cases [2].

Fractional excretion of calcium calculated from calcium and creatinine measurements on a 24-hour urine specimen and accompanying serum specimen can aid in differentiating the two conditions. Fractional excretion of calcium is calculated as [(24-hr urine calcium)/ (serum calcium)]/[(24-hr urine creatinine/ serum creatinine)], and a cut-point of <0.01 has been found to be indicative on FHH, while results >0.02 are more associated with PHPT [4]. However, 20-35% of patients with FHH may have a ratio above 0.01, and so genetic testing is recommended for those patients who fall within the "grey area" of 0.01 and 0.02 [6].

The patient had several features typical of FHH including young age, asymptomatic presentation, mildly elevated serum calcium (2.58mmol/l), low serum phosphate (0.71mmol/l), and mildly elevated PTH concentration (10.3pmol/l). Unfortunately, urinary fractional excretion of calcium was borderline at 0.01 and without the availability of genetic testing for mutations of the CaSR gene, a diagnosis of primary hyperparathyroidism was made based on the mildly elevated PTH concentration and parathyroid scintigraphy findings. While lack of genetic testing availability was a limitation in this work-up, it is a commonly encountered predicament in low-middle income settings like South Africa. However, other methods can be employed to assist in making a diagnosis, especially when differentiation of these conditions will have significant implications for patient management. Knowledge regarding the autosomal dominant nature of FHH could have been applied and testing of the immediate family members of the patient may have been useful pre-operatively, especially given that there was no indication to expedite the surgery. While this may not yield definitive results, it can be helpful and was eventually how the diagnosis was made.

This case demonstrated that the differentiation of PHPT and FHH may still be a diagnostic challenge in some circumstances. Importantly, the chemistry laboratory was not consulted during the course of this case, and this collaboration may have led to a different outcome. It is likely that more emphasis would have been placed on reaching a definitive diagnosis before invasive interventions were performed. Thorough review of the clinical and radiological findings as well as biochemical investigations

would likely have led to the suggestion of postponing the surgery until screening of family members for FHH can occur or arrangements could be made to outsource the genetic testing for FHH to an overseas facility.

While there are several published case reports of FHH, none that demonstrated the misdiagnosis of FHH as PHPT were identified. A case of FHH reported by Al-Ramdhan et al [9], demonstrates how the diagnosis of FHH was made both by testing family members of the index patient with basic serum and urine biochemical investigations as well as with genetic analysis.

The strength of this case report is that it demonstrates a classical presentation of a rare disease as well as how an inadequately investigated diagnostic dilemma and misdiagnosis led to an unnecessary surgical procedure. The limitation of this case report is that the chemistry laboratory was not actively involved in the decision making regarding diagnosis and management of this patient as well as the lack of availability of genetic testing. Regardless, relatively simple, easily accessible biochemistry investigations were integral to the generation of a differential as well as the eventual diagnosis in this patient and several of her family members.

Learning Points

- FHH is a benign condition that can be distinguished from PHPT clinically and biochemically, preventing unnecessary surgical procedures
- Screening of family members for FHH using routine biochemical investigations can aid diagnosis when genetic testing is unavailable
- Effective and collaborative communication between clinicians and the laboratory is crucial for optimal patient outcomes

Abbreviations

FHH – familial hypocalciuric hypercalcaemia
PHPT – primary hyperparathyroidism
PTH – parathyroid hormone
CaSR – calcium sensing receptor

Author Disclosures

The author wishes to declare that she has no personal or financial interests that may have influenced the writing of this article.

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