A Rare Case of Primary Hyperparathyroidism in Familial Hypocalciuric Hypercalcaemia

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ABSTRACT

Familial Hypocalciuric Hypercalcaemia (FHH), causing decreased activity of Calcium-Sensing Receptor (CaSR), is a rare genetic autosomal dominant condition. The abnormality causes mild hypercalcaemia with mildly elevated or normal parathyroid hormone (PTH) levels. FHH should be differentiated from primary hyperparathyroidism (PHPT). A 46-year woman, who presented with generalised aches and pains to her general practice physician, was referred to the endocrine department in 2008. Her serum calcium was 3.0 mmol/L (normal range (NR): 2.2 - 2.6 mmol/L) and PTH was 96 pmol/L (NR: 1.6 - 6.9 pmol/L). Her 24-hour urinary calcium was 2.8 mmol/24 hours (NR: 2.5 - 7.5 mmol/24 hour). Her nuclear imaging studies within a span of one year were consistent with the right, followed by the left parathyroid adenomas. She underwent two parathyroidectomies in an almost two-year period. In her last clinic consultation in 2022, she was found to have a genetic mutation causing FHH, Type 1.

Key Words: *Familial hypocalciuric hypercalcaemia*, *Hypercalcaemia*, *Primary hyperparathyroidism*, *Calcium sensing receptor*.

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INTRODUCTION

Familial Hypocalciuric Hypercalcaemia (FHH), causing decreased activity of Calcium-Sensing Receptor (CaSR), is a rare autosomal dominant genetic condition. The abnormality causes mild hypercalcaemia with mildly elevated or normal parathyroid hormone (PTH) levels.[1] In kidneys, this defect causes an increase in tubular reabsorption of calcium and magnesium leading to hypocalciuria, hypercalcaemia, and serum levels of magnesium in the upper normal range.[1-4]

As both the PTH and serum calcium levels are high in FHH, it is an important differential diagnosis of primary hyperparathyroidism (PHPT). This unique case report is about a patient who had simultaneous PHPT and FHH.

CASE REPORT

A 46-year woman has been seen by the Endocrine Department since 2008. Initially, she presented with generalised aches and pains and laboratory workup showed calcium of 3.0 mmol/L (normal range (NR): 2.2 - 2.6 mmol/L) and PTH was 96 pmol/L (NR: 1.6 - 6.9 pmol/L).

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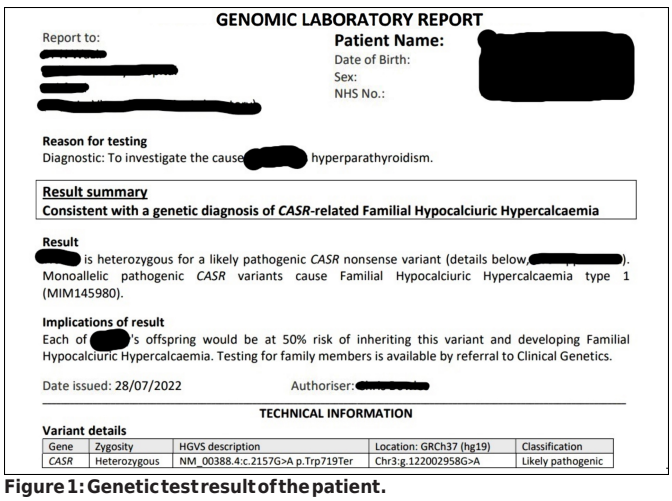
Her 24-hour urinary calcium was 2.8 mmol/24 hour (NR: 2.5 - 7.5 mmol/24 hour). Her sestamibi scan done in 2009 was consistent with right-lower parathyroid adenoma. In the same year, her right-lower parathyroidectomy was performed in accordance with the guidelines. Histology was consistent with parathyroid adenoma. Her laboratory parameters are shown in Table I. She had a recurrence of PHPT as suggested by high serum calcium and PTH levels along with subtraction imaging of I-123 suggestive of left-lower parathyroid adenoma. In 2011, she underwent another parathyroidectomy. In the histology performed on the specimen after the procedure, three parathyroid glands were identified, two of which appeared to be unusually large. Her previous history and biochemical tests along with the histology at that time, made the histologists believe that rather than multiple adenomas, she had parathyroid hyperplasia. Her serum calcium and PTH levels either remained elevated or at the upper limit of normal throughout despite two parathyroidectomies. She continued to remain symptomatic and was treated conservatively with routine checks of her serum calcium and PTH levels alongside the prescription of Cinacalcet for symptomatic relief. In June 2021, a dual isotope nuclear medicine study with digital subtraction was suggestive of right-lower parathyroid adenoma. Just before her last clinical appointment, 24-hour urinary calcium was 1.9 mmol/24 hours (NR: 2.5-7.5 mmol/24 hours), but her vitamin D level was 31 nmol/L (Adequate = 50-75 nmol/L). Throughout the course of her illness, the Calcium Creatinine Clearance ratio (CCCR) was never calculated. In the last clinical consultation in 2022, her serum calcium was 2.7 mmol/L and PTH was 9.3 pmol/L. She was still symptomatic of hypercalcaemic symptoms such as generalised aches and pains.

Because of her onset of PHPT at a younger age, it was decided to conduct a complete genetic test panel to rule out genetic hyperparathyroidism syndromes. The genetic test was consistent with the *CaSR* gene heterozygous nonsense mutation giving the diagnosis of *CASR*-related FHH 1 (Figure 1).

Table I: Laboratory parameters of the patient.

Date	S Calcium (mmol/L) NR = 2.2-2.6	PTH (pmol/L) NR = 1.6-6.9	Vit D (nmol/L) Adequate = 50-75	24 hour Ur Cal (mmol/24 hours) NR = 2.5-7.5
29/12/2008	3.0	96		
02/01/2009				2.8
02/03/2009	3.0	117		
22/06/2009	3.1			
04/01/2010	2.9	46		
16/08/2010	2.8			
08/12/2010	2.6			
31/01/2011	2.8			
06/05/2011	2.7			
10/06/2011	2.7	8.6		
04/07/2011	2.7	7.3		
05/09/2011	2.7	5.6		
30/11/2011				2.4
01/12/2011	2.6	11.0		
05/03/2012	2.7	5.1		
10/08/2012	2.7	6.2		
13/09/2012	2.7	5.0		
05/03/2013	2.9	3.8		
06/02/2013		4.5		
15/03/2013		3.1		
02/05/2013	2.7	4.7		
28/08/2013	2.8	6.1		
12/05/2014	2.6	4.8		
25/11/2015	2.7	10.2		
04/04/2016	2.6			
09/06/2016				4.3
21/07/2017	2.6			
24/08/2018			49	
27/06/2018	2.6	8.3		
11/04/2019	2.8	6.7	<18	
27/02/2020	2.7	11.0		
04/08/2020	2.7	10.2	78	
19/01/2021	2.5	7.3		
11/11/2021	2.7	9.3	31	1.9
14/06/2022	2.6		49	

S Calcium = Serum Calcium, PTH = Parathyroid Hormone, NR = Normal Range, Vit D = Vitamin D, 24 hour Ur Cal = 24-hour Urinary Calcium.



GENOMIC LABORATORY REPORT

Report to:

[redacted]

Patient Name: [redacted]

Date of Birth:

Sex:

NHS No.:

Reason for testing

Diagnostic: To investigate the cause [redacted] hyperparathyroidism.

Result summary

Consistent with a genetic diagnosis of *CASR*-related Familial Hypocalciuric Hypercalcaemia

Result

[redacted] is heterozygous for a likely pathogenic *CASR* nonsense variant (details below, [redacted]). Monoallelic pathogenic *CASR* variants cause Familial Hypocalciuric Hypercalcaemia type 1 (MIM145980).

Implications of result

Each of [redacted]'s offspring would be at 50% risk of inheriting this variant and developing Familial Hypocalciuric Hypercalcaemia. Testing for family members is available by referral to Clinical Genetics.

Date issued: 28/07/2022 Authoriser: [redacted]

TECHNICAL INFORMATION

Variant details

Gene	Zygosity	HGVS description	Location: GRCh37 (hg19)	Classification
CASR	Heterozygous	NM_00388.4:c.2157G>A p.Trp719Ter	Chr3:g.122002958G>A	Likely pathogenic

Figure 1: Genetic test result of the patient.

DISCUSSION

FHH is a rare benign inherited condition that usually does not require surgery in the form of parathryoidectomy. It is caused by a mutation in *CaSR* gene mutation causing hypercalcaemia in the face of high PTH levels. In this biochemical scenario, it is an important differential diagnosis of PHPT. Conversely, PHPT requires surgical intervention in the form of parathyroidectomy as per the published guidelines.[5]

In the last clinic consultation, our patient being treated for PHPT, turned out to have simultaneous FHH, only after genetic testing. She had been treated by different physicians but until her last consultation in 2022, genetic testing was not done. FHH is a very rare genetic disease. Concomitant FHH and PHPT are even a rarer occurrence and research about the association of these two conditions has been very limited. The biochemical picture of these two clinical entities occurring together is elevated serum calcium and PTH levels, hypophosphataemia, and low urinary calcium levels. In our patient, 24-hour urinary calcium was never above the upper limit of normal, and on one occasion it was low when she was having vitamin D insufficiency. Alkundi *et al*. reported a similar case.[6] Another case reported the occurrence of PHPT secondary to parathyroid adenoma in a middle-aged male patient.[7] Similarly, Russell *et al*. recently reported the occurrence of parathyroid adenoma causing PHPT in a patient diagnosed to have FHH caused by *CaSR* mutation.[8]

As both the PTH and serum calcium levels are high in FHH, it is an important differential diagnosis of PHPT. Biochemically, CCCR is commonly used to differentiate between FHH and PHPT. CCCR was never calculated in our patient throughout the course of her illness. CCCR calculation might have given the clue towards the occurrence of co-existing FHH and the genetic testing could have been done earlier. Urinary calcium excretion is less than 2.5 mmol/day in approximately 80% of FHH individuals and their CCCR is less than 0.01.[4] On the contrary, CCCR is more than 0.02 in PHPT patients while in around 20% of such patients who have vitamin D deficiency, CCCR is more than 0.01.[4] Even if a patient has a classical constellation of symptoms, serum parameters and imaging studies suggestive of PHPT, CCCR and 24-hour urinary calcium need attention to pay to because very rarely these conditions can co-exist.

Although very rare, FHH, Type 1 is associated with PHPT and the genetic testing panel should include testing for this condition in young patients with established PHPT. This becomes even more important when there is persistently raised PTH despite parathyroidectomy. Occurrence of PHPT either in the form of adenoma or hyperplasia on a background of FHH is being reported in increasing numbers now. The association, if any, remains to be scientifically explained.

PATIENT'S CONSENT:

Written informed consent was taken from the patient to publish the data concerning this case.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
NW: Concept, design, interpretation of data, analysis, and drafting of the manuscript.
AA: Acquisition of data and revision of the work critically.
Both authors approved the final version of the manuscript to be published.

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