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A Novel Genetic Variant Resulting in Familial Hypocalciuric Hypercalcaemia

A. K. Coughlan, F. Khan, M. J. Brassill

Department of Endocrinology, Tipperary University Hospital, Clonmel, Co. Tipperary, Ireland.

Abstract

Presentation

A 17-year-old male was referred to the endocrinology service with an incidental finding of hypercalcaemia. Over the course of the previous year his calcium ranged from 2.64-2.77mmol/L (reference range: 2.2-2.6mmol/L) in the setting of a normal/low parathyroid hormone (PTH) of 14-35pg/ml (reference range: 15-65pg/ml).

Diagnosis

Following biochemical confirmation of hypocalciuric hypercalcaemia he was referred for molecular genetic analysis which showed a heterozygous variant in the CASR gene previously undescribed in the literature: c.491A>G; p.GIn164Arg.

Treatment

The patient and his parents were reassured with regard to the benign nature of the condition and counselled with regard to its inheritance.

Discussion

Though there is little data on this genetic variant, it is assumed to have caused familial hypocalciuric hypercalcaemia (FHH) in this gentleman. FHH is an important differential in hypercalcaemia as it can be misdiagnosed as primary hyperparathyroidism, potentially leading to unnecessary surgical intervention.

Introduction

FHH is a rare autosomal dominant disorder. It results from an inactivating mutation of the calcium-sensing receptor (CASR) on parathyroid and renal cells, in the loop of Henle and distal convoluted tubule, causing a requirement for higher calcium levels in order to suppress PTH release. It is usually benign, asymptomatic, and characterised by mild hypercalcaemia, hypocalciuria, hypermagnesaemia, hypophosphataemia and PTH levels mildly elevated or within reference range.[1] It is an important differential diagnosis in hypercalcaemia because misdiagnosis as primary hyperparathyroidism, the commonest cause of hypercalcaemia with normal or elevated PTH, may result in unnecessary parathyroidectomy.[2] Low urinary calcium to creatinine clearance ratio is a helpful indicator of FHH, but observed ranges can overlap that of primary hyperparathyroidism.[3]

Case Report

We present the case of a 17 year old gentleman referred to endocrinology due to an incidental finding of hypercalcaemia of 2.64-2.77mmol/L (2.2-2.6mmol/L) over the previous one year. Simultaneous PTH levels had been in the lower half of the normal range, or just below normal, ranging from 14-35pg/ml (15-65pg/ml). Of note a normal calcium level of 2.65mmol/L (2.2 -2.7mmol/L) had been noted 4 years prior to his first recorded elevated level using a paediatric reference range.

At presentation the patient was asymptomatic, with no history of renal or gastrointestinal signs or symptoms. He had experienced intermittent palpitations but cardiac workup including 24 hour holter monitor, cardiac event recorder, echocardiogram and exercise stress test showed no abnormalities. He was taking no regular medications. As the patient had been adopted, a full family history was not available. No history of calcium disorders was conveyed to his adoptive parents in the family medical history they had received however.

A 25-OH Vitamin D level was adequate at 80.8nmol/L. Serum magnesium and phosphate levels were normal at 0.89mmol/L (0.7-1.0mmol/L) and 1.21mmol/L (0.8-1.5mmol/L) respectively. Chest x-ray was normal with no signs of sarcoidosis. An initial 24-hour urine collection prior to referral had shown calcium excretion of 1.8mmol/24 hours (2.5-7.5mmol/24 hours).

A 24 hour urine collection was repeated to measure both calcium and creatinine excretion. This showed a calcium excretion of 0.89mmol/24 hours (2.5-7.5mmol/24 hours) and a creatinine excretion of 9.1mmol/24 hours (9-19 mmol/24 hours). Simultaneous serum calcium (2.77mmol/L) and creatinine (58umol/L) levels were taken to calculate urinary calcium:creatinine clearance ratio. This was calculated as 0.002, with a value < 0.01 highly suggestive of FHH. At this point molecular genetic analysis was requested to confirm FHH. (See table 1 for laboratory results.)

Table 1. Lab Results

		2 months prior	10 months prior
Calcium (2.2-2.6 mmol/L)	2.77 mmol/L	2.69 mmol/L	2.64 mmol/L
PTH (15-65 pg/ml)	14 pg/ml	35 pg/ml	21.3 pg/ml
25-OH Vitamin D	80.8 nmol/L		
Magnesium (0.7-1 mmol/L)	0.89 mmol/L		
Phosphate (0.8-1.5 mmol/L)	1.21 mmol/L		
24-hour urine collection:			
• Calcium	0.89 mmol/24hours		
• Creatinine	9.1 mmol/24hours		
Simultaneous serum collection:			
• Calcium (2.2-2.6 mmol/L)	2.77 mmol/L		
• Creatinine (62-106 umol/L)	58 umol/L		
Calculated urinary calcium:creatinine clearance ratio	0.002		

The coding and flanking intronic regions of the CASR gene were enriched using in-solution hybridisation technology and sequenced using the Illumina HiSeq system. At least one rare variant was then re-sequenced using conventional Sanger sequencing, to provide independent confirmation. Variants were classified and reported based on ACMG/ACGS-2020v4.01 guidelines.[4] This testing showed one heterozygous variant in the CASR gene with the substitution of glutamine for arginine at codon 164 of the CASR protein (c.491A>G; p.GIn164Arg). This variant has not been previously described in the literature.

Discussion

Familial hypocalciuric hypercalcaemia is an important differential diagnosis in the investigation of hypercalcaemia. A 24 hour urine collection for calcium and creatinine excretion is most accurate to calculate the calcium:creatinine clearance ratio, which is equivalent to the fractional excretion of calcium. Although this genetic variant is formally classified as a variant of unknown significance it is likely to be pathogenic in this case, in keeping with the clinical diagnosis of FHH. While this variant has not been described previously in the literature, a different amino acid substitution at the same codon (c.490C>A; p.Gin164Lys) has been reported in a father and daughter with mild hypercalcaemia.[5] This supports the likelihood of a variant in this codon leading to the presentation of clinical FHH. The patient and his parents were counselled as to the benign nature of the condition and its inheritance.

Declaration of Conflicts of Interest:
None to declare.

Corresponding Author:
Dr Aoife Katie Coughlan,
Department of Endocrinology,
Tipperary University Hospital,
Clonmel,
Co. Tipperary,
Ireland.
E-Mail: akcoughlan@hotmail.com

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