Scientific Research Publishing

Open Journal of Endocrine and Metabolic Diseases, 2025, 15(8), 154-160
https://www.scirp.org/journal/ojemd
ISSN Online: 2165-7432
ISSN Print: 2165-7424

Clinical Presentation and Diagnostic Challenges of Familial Hypocalciuric Hypercalcemia Type 3: A Case Report

Joseph Saliba, Jessica Saliba, Carol Diane Attard, Mario Joseph Cachia, Alison Galea

Department of Medicine, Diabetes and Endocrinology Mater Dei Hospital, Msida, Malta
Email: Jsal0011@gmail.com

How to cite this paper: Saliba, J., Saliba, J., Attard, C.D., Cachia, M.J. and Galea, A. (2025) Clinical Presentation and Diagnostic Challenges of Familial Hypocalciuric Hypercalcemia Type 3: A Case Report. *Open Journal of Endocrine and Metabolic Diseases*, **15**, 154-160.
https://doi.org/10.4236/ojemd.2025.158015

Received: July 8, 2025
Accepted: August 25, 2025
Published: August 28, 2025

Copyright © 2025 by author(s) and Scientific Research Publishing Inc.
This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).
http://creativecommons.org/licenses/by/4.0/

Open Access

Abstract

We report the case of a male patient in his early thirties presenting with persistent hypercalcemia and a notable family history of hypercalcemia. Both his mother and brother were diagnosed with primary hyperparathyroidism and had undergone parathyroidectomy. Initial biochemical investigations demonstrated elevated serum calcium and parathyroid hormone levels, but low urinary calcium excretion, raising suspicion for familial hypocalciuric hypercalcemia (FHH). Genetic testing subsequently revealed a pathogenic mutation in the AP2S1 gene, confirming FHH type 3. This case highlights the diagnostic challenges in distinguishing FHH from primary hyperparathyroidism and emphasizes the importance of genetic analysis in guiding appropriate management.

Keywords

Familial Hypocalciuric Hypercalcaemia, Hypercalcaemia, Primary Hyperparathyroidism

1. Introduction

Familial hypocalciuric hypercalcemia (FHH) is a rare genetic disorder inherited in an autosomal dominant manner. It consists of three subtypes that are clinically indistinguishable from one another and are caused by different gene mutations. Approximately 65% of the cases have FHH type 1. FHH type 1 is caused by inactivating mutations in the calcium-sensing receptor (CaSR) gene. (1) On the other hand, FHH type 2 is caused by inactivation of the G-protein subunit α11 (GNA11) gene, which is responsible for the CaSR signal transduction [1].

FHH type 3 accounts for approximately 20% of all FHH cases and has a median

age at diagnosis of 34 years [2] [3]. It is caused by activating mutations in the adaptor-related protein complex two sigma subunit 1 (AP2S1) gene, located on chromosome 19 [4].

All known missense mutations in the AP2S1 gene are associated with disease, involving the substitution of the arginine residue at position 15 (Arg15), specifically: Arg15Cys, Arg15His, and Arg15Leu [4]. This mutation decreases the sensitivity of CaSR-expressing cells to extracellular calcium and reduces CaSR endocytosis [2]. In the parathyroid glands, normal or elevated calcium levels are misinterpreted as low, resulting in inappropriate secretion of parathyroid hormone (PTH), which in turn leads to mild hypercalcemia. Meanwhile, in the kidneys, it will result in reduced calcium excretion. This combination will result in hypocalciuric hypercalcemia [5].

Higher elevations of serum albumin adjusted-calcium concentrations were noted in Arg15Leu mutations than in those with Arg15Cys and Arg15His AP2S1 mutations [4].

2. Case Presentation

A gentleman in his early thirties, was referred to the endocrine department with persistent hypercalcaemia (3.05 mmol/l, reference range: 2.05 - 2.60 mmol/l). He had a history of type 2 diabetes mellitus, neonatal cerebral hypoxia, alcohol abuse, and depression. Approximately seven years prior, the patient began experiencing seizures and was initiated on sodium valproate therapy. Magnetic resonance imaging (MRI) of the brain was unremarkable, with no evidence of intracranial calcifications. He had no history of lithium use or treatment with thiazide diuretics.

The patient had a positive family history of hypercalcemia, with two first-degree relatives—his mother and brother—previously diagnosed with primary hyperparathyroidism. Both patients were considered suitable candidates for surgery, as their corrected serum calcium levels exceeded 1 mg/dL above the upper limit of normal, and they were under 50 years of age at the time of evaluation. Neither exhibited skeletal nor renal involvement. Both underwent parathyroidectomy; however, cinacalcet therapy was initiated postoperatively due to persistently elevated corrected calcium levels. Genetic testing was not performed prior to surgery

On examination, the patient had no signs of bone tenderness, nephrolithiasis, abdominal pain, or muscle weakness. The patient denied symptoms such as polyuria, constipation, nausea, or mood changes. However, he did report experiencing depression associated with alcoholism and suicidal ideations. He had no history of pancreatitis. Physical examination of the abdomen, respiratory, and cardiovascular systems revealed no abnormalities.

The first set of blood panel showed a high corrected calcium level of 3.05 mmol/l (reference range: 2.05 - 2.60 mmol/l), normal phosphate level of 1.12 mmol/l (reference range: 0.87 - 1.45 mmol/l) and borderline low serum 25-hydroxyvitamin D level of 28 ng/ml (reference range: 30 - 100 ng/mL). Serum magnesium was normal at 1.0 mmol/L (0.65 - 1.05 mmmol/L).

Parathyroid hormone (PTH) was mildly elevated at 67 pg/ml (reference range: 15 – 65 ng/ml). The patient's serum 25-hydroxyvitamin D level was normalised to 33 ng/ml following supplementation with Vitamin D. However, his corrected serum calcium remained significantly elevated at 2.92 mmol/l and his PTH level remained mildly raised as well (67 pg/ml, range 15 - 65 pg/ml).

An ultrasound neck did not reveal any enlarged parathyroid glands. A subsequent sestamibi and pertechnetate parathyroid scan showed no abnormal areas of increased tracer uptake indicative of any parathyroid adenomas, which were also not evident on a computed tomography scan of the neck and thorax. Dual x-ray absorptiometry (DEXA) scan revealed osteopenia with bone mineral density with a T-score of −1.4 at the lumbar spine and −1.3 at the femoral neck.

The main differential diagnosis at this point was familial primary hyperparathyroidism (PHPT), with familial isolated PHPT being most likely given the absence of extra parathyroid manifestations in both the patient and his family, or more likely familial hypocalciuric hypercalcaemia in view of the low 24-hour urinary calcium.

The patient was initially treated with a 60 mg dose of pamidronate disodium; however, his corrected calcium level remained elevated at 3.14 mmol/L. Normocalcaemia was subsequently achieved with 30 mg of cinacalcet administered twice daily.

A 24-hour urine collection for calcium and creatinine was performed. The results showed a low urine calcium level of 1.42 mmol/L/24 hours (reference range: 2.5 - 8 mmol/24 hours), a low random urine calcium of 0.39 mmol/L (reference range: 1.7 - 5.3 mmol/L), and a urine creatinine of 1.86 mmol/L (reference range: 3.45 - 22.9 mmol/L). The calculated urine calcium-to-creatinine clearance ratio (CCCR) was 0.0163.

The patient was referred to the genetics clinic for counseling and genetic testing for FHH. The genetic panel included analysis of the CaSR, AP2S1, and GNA11 genes. The testing identified a heterozygous mutation in the AP2S1 gene, specifically an Arg15Leu substitution, consistent with FHH type 3.

The patient has now been followed up for seven years. During this period, we observed that the corrected calcium and PTH levels remained within the normal range on cinacalcet 30 mg, which was eventually increased to thrice daily. A repeat DEXA scan five years after starting treatment has revealed improvement of the osteopenia at the femoral neck; from a T-score of −1.3 to −0.6. However, the T-score at the lumbar spine remained the same at −1.4. His epilepsy remained under control, and he had no further admissions with seizures.

Regarding his depression, he had remained stable over the past six years, with no further admissions for suicidal ideation, and had regular follow-up appointments with his psychiatrist. His renal function remains normal with an estimated glomerular filtration rate of 88 mls/min/1, 73 m^2 with no detectable albuminuria.

3. Discussion

We report the case of a gentleman in his early thirties with a history of hypercal-

caemia and depression, a positive family history of hypercalcaemia, and a germline Arg15Leu substitution mutation in the AP2S1 gene.

FHH is a benign disorder that is not associated with end-organ damage and, consequently, does not necessitate therapeutic intervention [6]. Patients with FHH type 3 were noted to have higher levels of serum calcium concentrations and lower levels of urinary calcium excretion than those with FHH type 1 [3].

In our case, the patient had a history of depression and suicidal ideations. Hypercalcaemia is known to cause neuropsychiatric dysfunction. Patients with hypercalcaemia may present with depression, anxiety, and cognitive changes. In more severe cases, patients may experience psychosis, confusion, altered mental status, lethargy, and coma [7]. In a report by Hendy *et al.*, three patients were identified with AP2S1 gene mutations. Among them, one individual carrying the Arg15Leu mutation, exhibited cerebral palsy along with global developmental delay. The other two cases with Arg15Leu and Arg15Cys mutations were diagnosed with major depressive disorder and an unspecified psychiatric condition, respectively [8].

Significant incidence of cognitive and behavioural disorders was reported in patients with FHH 3 [9] [10]. Six children, 0.1 to 8 years of age with FHH 3 were reported to have neurodevelopmental problems ranging from global developmental delay (n = 4), learning difficulty at school (n = 3), dyslexia (n = 1) and isolated mild motor delay (n = 1). Moreover, three children were diagnosed with autism spectrum disorder (ASD) and one with attention deficit hyperactivity disorder (ADHD). Relatives which were affected with FHH 3 were also noted to have mild to moderate learning difficulties, hyperactivity, and dyslexia [9].

Differentiating PHPT from familial hypocalciuric hypercalcaemia (FHH) can be challenging but is essential, as PHPT is potentially curable through parathyroidectomy, whereas FHH does not respond to surgical treatment [11]. Both PHPT and FHH can present with mild hypercalcaemia and elevated PTH. Other conditions that can present with hypercalcemia and elevated PTH, and should be considered in the differential diagnosis, include the use of thiazide diuretics, lithium therapy, and rare cases of ectopic PTH secretion [12].

A urinary calcium-to-creatinine clearance ratio (CCCR) less than 0.01 suggests familial hypocalciuric hypercalcaemia (FHH), whereas a ratio greater than 0.02 is more consistent with primary hyperparathyroidism (PHPT) [11]. Unfortunately, in our case, the calcium-to-creatinine clearance ratio (CCCR) was not calculated prior to starting treatment with cinacalcet, however, he had a very low 24-hour urinary calcium excretion in the presence of normal 25-hydroxyvitamin D levels. Approximately 20% of patients with FHH have a CCCR greater than 0.01, making urinary calcium levels unreliable for diagnosing FHH. The most accurate method to confirm FHH is through genetic testing for mutations in the CaSR, AP2S1, and GNA11 genes [1] [13] [14].

Cinacalcet is a calcimimetic agent that targets the CaSR, leading to a reduction in PTH secretion and serum calcium levels. Approximately 75% of patients with

FHH can achieve normalization of serum calcium concentrations with cinacalcet treatment [15]. Cinacalcet has been reported to lower serum calcium levels by approximately 10% in a patient with FHH type 3 [16]. In our case, treatment with cinacalcet resulted in about a 15% reduction in calcium levels, leading to a normal serum calcium. Therefore, cinacalcet may represent a potential therapeutic option for FHH, particularly in cases like FHH3 where serum calcium remains persistently elevated.

4. Conclusion

This case highlights the diagnostic challenges in distinguishing FHH from PHPT, particularly in patients with a positive family history and overlapping biochemical features. The presence of hypercalcemia with inappropriately normal or elevated PTH and low urinary calcium excretion should prompt consideration of FHH. In this patient, genetic testing confirmed FHH type 3 due to an AP2S1 Arg15Leu mutation. This diagnosis prevented unnecessary surgical intervention and guided appropriate medical management with cinacalcet, which effectively normalized serum calcium levels. Furthermore, the patient's psychiatric symptoms raise the possibility of neuropsychiatric involvement in FHH3, as previously described in the literature. This case underscores the importance of genetic evaluation in cases of familial hypercalcemia and supports the role of cinacalcet as a therapeutic option in symptomatic patients with FHH3.

5. Learning Points

- Parathyroidectomy is not curative in FHH and treatment with cinacalcet is indicated if there is end-organ damage or symptoms, which can be ameliorated.
- It is important to calculate the calcium creatinine clearance ratio (CCCR) by collecting and measuring 24-hour urinary samples for calcium and creatinine excretion simultaneously with serum calcium and creatinine to help assess FHH, though it is limited by reduced diagnostic sensitivity and specificity. Genetic diagnosis is mandatory for confirmatory testing.

24-hour urinary calcium excretion is reduced in the presence of Vitamin D insufficiency/deficiency, renal impairment and thiazide diuretics, while it is increased in pregnancy. Hence, CCCR cannot be calculated in such instances.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Lee, J.Y. and Shoback, D.M. (2018) Familial Hypocalciuric Hypercalcemia and Related Disorders. *Best Practice & Research Clinical Endocrinology & Metabolism*, **32**, 469-482.

[2] Nesbit, M.A., Hannan, F.M., Howles, S.A., Reed, A.A.C., Cranston, T., Thakker, C.E., *et al.* (2012) Mutations in AP2S1 Cause Familial Hypocalciuric Hypercalcemia Type

3. *Nature Genetics*, **45**, 93-97. https://doi.org/10.1038/ng.2492

[3] Vargas-Poussou, R., Mansour-Hendili, L., Baron, S., Bertocchio, J., Travers, C., Simian, C., *et al.* (2016) Familial Hypocalciuric Hypercalcemia Types 1 and 3 and Primary Hyperparathyroidism: Similarities and Differences. *The Journal of Clinical Endocrinology & Metabolism*, **101**, 2185-2195. https://doi.org/10.1210/jc.2015-3442

[4] Hannan, F.M., Howles, S.A., Rogers, A., Cranston, T., Gorvin, C.M., Babinsky, V.N. *et al.* (2015) Adaptor Protein-2 Sigma Subunit Mutations Causing Familial Hypocalciuric Hypercalcaemia Type 3 (FHH3) Demonstrate Genotype-Phenotype Correlations, Codon Bias and Dominant-Negative Effects. *Human Molecular Genetics*, **24**, 5079-5092.

[5] Pearce, S.H., Trump, D., Wooding, C., Besser, G.M., Chew, S.L., Grant, D.B., *et al.* (1995) Calcium-Sensing Receptor Mutations in Familial Benign Hypercalcemia and Neonatal Hyperparathyroidism. *Journal of Clinical Investigation*, **96**, 2683-2692. https://doi.org/10.1172/jci118335

[6] Egbuna, O.I. and Brown, E.M. (2008) Hypercalcaemic and Hypocalcaemic Conditions Due to Calcium-Sensing Receptor Mutations. *Nature Clinical Practice Endocrinology & Metabolism*, **4**, 107-118.

[7] Nagy, L., Mangini, P., Schroen, C., Aziz, R. and Tobia, A. (2020) Prolonged Hypercalcemia-Induced Psychosis. *Case Reports in Psychiatry*, **2020**, Article ID: 6954036. https://doi.org/10.1155/2020/6954036

[8] Hendy, G.N., Canaff, L., Newfield, R.S., Tripto-Shkolnik, L., Wong, B.Y.L., Lee, B.S.P., *et al.* (2014) Codon Arg15 Mutations of the AP2S1 Gene: Common Occurrence in Familial Hypocalciuric Hypercalcemia Cases Negative for Calcium-Sensing Receptor (*CASR*) Mutations. *The Journal of Clinical Endocrinology & Metabolism*, **99**, E1311-E1315. https://doi.org/10.1210/jc.2014-1120

[9] Szalat, A., Shpitzen, S., Tsur, A., Zalmon Koren, I., Shilo, S., Tripto-Shkolnik, L., *et al.* (2017) Stepwise Casr, AP2S1, and GNA11 Sequencing in Patients with Suspected Familial Hypocalciuric Hypercalcemia. *Endocrine*, **55**, 741-747. https://doi.org/10.1007/s12020-017-1241-5

[10] Chinoy, A., Nicholson, J., Skae, M., Hannan, F.M., Thakker, R.V., Mughal, M.Z., *et al.* (2023) Neurodevelopmental Abnormalities in Patients with Familial Hypocalciuric Hypercalcemia Type 3. *The Journal of Pediatrics*, **257**, Article ID: 113367. https://doi.org/10.1016/j.jpeds.2023.02.013

[11] Bilezikian, J.P., Potts, J.T., Fuleihan, G.E., Kleerekoper, M., Neer, R., Peacock, M., *et al.* (2002) Summary Statement from a Workshop on Asymptomatic Primary Hyperparathyroidism: A Perspective for the 21st Century. *The Journal of Clinical Endocrinology & Metabolism*, **87**, 5353-5361. https://doi.org/10.1210/jc.2002-021370

[12] Bilezikian, J.P., Khan, A.A., Silverberg, S.J., Fuleihan, G.E., Marcocci, C., Minisola, S., *et al.* (2020) Evaluation and Management of Primary Hyperparathyroidism: Summary Statement and Guidelines from the Fifth International Workshop. *Journal of Bone and Mineral Research*, **37**, 2293-2314. https://doi.org/10.1002/jbmr.4677

[13] Medline Plus Genetics (n.d.) GNA11 Gene. U.S. National Library of Medicine. https://medlineplus.gov/genetics/gene/gna11/

[14] Parathyroid (2021) FHH and Diagnosing FHH. Familial Hypocalciuric Hypercalcemia (FHH); Low Urine Calcium. Norman Parathyroid Center. https://www.parathyroid.com/FHH.htm

[15] Marx, S.J. (2017) Calcimimetic Use in Familial Hypocalciuric Hypercalcemia—A Perspective in Endocrinology. *The Journal of Clinical Endocrinology & Metabolism*, **102**, 3933-3936. https://doi.org/10.1210/jc.2017-01606

[16] Kerut, S., Kovvuru, K.R., Yanes-Cardozo, L. and Garla, V.V. (2020) Familial Hypocalciuric Hypercalcaemia Type 3: AP2S1 Missense Mutation. *BMJ Case Reports*, **13**, e236631. https://doi.org/10.1136/bcr-2020-236631