CASE REPORT

Nephrotic Syndrome Complicated with Familial Hypocalciuric Hypercalcemia in an Infant: A Case Report and Comprehensive Literature Review

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ABSTRACT

Background • Nephrotic syndrome, a prevalent childhood glomerular disorder, manifests with proteinuria, hypoalbuminemia, edema, and hypercholesteremia. Hypercalcemia, though rare, occasionally complicates these cases. Familial hypocalciuric hypercalcemia, an autosomal dominant disorder, is characterized by lifelong hypercalcemia, hypocalciuria, and normal or elevated parathyroid hormone levels due to loss-of-function mutations.

Case Presentation • We detail a 2-year-old girl with nephrotic syndrome whose proteinuria responded effectively to steroid therapy without side effects. Hypercalcemia emerged after one month, prompting a familial history investigation, revealing a predisposition to hypercalcemia. Genetic analysis identified a heterozygous mutation c.1394G>A (p.R465Q) in the calcium-sensing receptor gene, shared among the patient, her grandmother, her father, and one sister. Notably, hypercalcemia required no intervention.

Conclusions • This case report is the first documenting familial hypocalciuric hypercalcemia in a child with primary nephrotic syndrome and delineates the familial pedigree. While familial hypocalciuric hypercalcemia is infrequent, our findings affirm its generally benign nature. A critical aspect of patient care involves monitoring for potential complications, including acute pancreatitis or chondrocalcinosis. The indispensability of genetic studies in both diagnosis and the differentiation of related conditions is underscored, emphasizing their pivotal role in enhancing our understanding of this rare yet clinically significant disease. Continued research is imperative for advancing knowledge and improving clinical management. (*Altern Ther Health Med.* [E-pub ahead of print.])

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BACKGROUND

Nephrotic syndrome (NS) represents a glomerular disorder primarily defined by prominent proteinuria, hypoalbuminemia, edema, and hyperlipidemia.[1] This condition can be categorized into three main types: primary, secondary, and hereditary,[2] with childhood NS as prevalent chronic kidney disease. The incidence of childhood NS is reported at 4.71 per 100 000.[3] Familial hypocalciuric hypercalcemia (FHH) stands out as an autosomal dominant disorder featuring hypercalcemia alongside hypocalcemia, secondary hyperparathyroidism, and osteomalacia.[4] While distinct from NS, this condition underscores the complexity of renal and calcium homeostasis. The coexistence of NS and FHH in children is a rare but noteworthy occurrence.

Urinary calcium excretion and the calcium creatinine clearance ratio (CCCR) levels play a pivotal role in the differential diagnosis of FHH.[5] These parameters serve as crucial indicators, contributing significantly to accurately identifying FHH. The current treatment protocol for FHH involves the surgical removal of hyperplastic parathyroid glands. Postoperatively, oral calcium and vitamin D supplementation are administered to sustain normal blood calcium levels, ensuring the overall efficacy of the intervention.[6] This approach underscores the necessity for a multifaceted therapeutic strategy in managing FHH.

Loss-of-function mutations in the calcium-sensing receptor (*CASR*), G protein subunit alpha 11 (GNA11), and adaptor-related protein complex 2 subunit sigma 1 (AP2S1) are responsible for FHH types 1-3 (FHH1-3), respectively. Notably, FHH1 patients exhibit low renal Ca^{2+} excretion alongside normal or elevated parathyroid hormone (PTH) and Mg^{2+} levels.[7] This distinctive biochemical profile characterizes FHH1, which, despite its rarity, manifests as a generally benign disorder, typically presenting as asymptomatic.[6,7]

The *CASR* plays a crucial role in regulating PTH release and calcium reabsorption. When the *CASR* gene undergoes

functional alterations, it becomes desensitized to extracellular Ca^{2+}, leading to elevated PTH levels. Consequently, patients experience reduced urine calcium excretion and develop higher serum Ca^{2+} levels.[8]

Mutations in the *CASR* gene can result in various calcium disorders, including FHH, neonatal severe hyperparathyroidism (NSHPT), autosomal-dominant hypocalcemia type-1 (ADH1), and Bartter's syndrome type V.[9,10] In NSHPT, individuals with inactivating mutations in the *CASR* gene are typically homozygotes, while heterozygotes commonly develop FHH.[11] Notably, some cases of FHH1 involve homozygous individuals, who may exhibit a milder loss of function compared to their heterozygous counterparts.[12]

In this study, we reported a *CASR* mutation discovered in a girl with FHH, initially identified due to the presentation of NS during early childhood. Our findings underscore the significance of genetic analysis as the gold standard in distinguishing FHH from other potential causes of hypercalcemia.

CASE PRESENTATION

Presentation and Initial Diagnosis of Nephrotic Syndrome (NS)

In August 2020, a 2-year-old girl was admitted due to a three-month history of increasing eye swelling. Laboratory investigations revealed significant abnormalities, including proteinuria (0.74 g/24 h), reduced serum albumin (22.6 g/L), and hypercholesteremia (7.76 mmol/L). These clinical presentations, along with the results detailed in Table 1, led to the diagnosis of NS.

Management and Follow-up of Steroid-Sensitive NS

The patient was initiated on prednisone treatment at 2 mg/kg/day p.o. post-diagnosis, indicating steroid-sensitive NS. Remarkably, within one week of treatment, NS symptoms significantly improved, with eyelid edema and proteinuria disappearing. The patient was then discharged, and monthly follow-ups ensued, during which no complications were observed. Laboratory tests were conducted regularly, allowing for the adjustment of the prednisone dose throughout the course of treatment.

Hypercalcemia Detection And Family Screening

Hypercalcemia Observation and Family History. During a one-month follow-up, the patient exhibited hypercalcemia, with elevated serum calcium levels ranging from 2.63 to 2.95 mmol/L (reference range 2.15-2.55 mmol/L). Urine calcium was 1.08 mmol/L (reference range 2.5-7.5 mmol/L). Serum magnesium, phosphorus, and PTH levels were reported as normal (Table 2). Despite the high serum calcium, the patient remained asymptomatic. Further investigation revealed a family history of hypercalcemia in the patient's grandmother, father, and two sisters (Figure. 1A). Notably, all family members were asymptomatic and required no intervention.

Table 1. Laboratory Parameters (August 2020)

Laboratory Parameter	Result	Normal Value
Total leucocytes (×10⁹/L)	6.79	5.5-9.5
Hemoglobin (g/L)	139	115-150
Platelets (×10⁹/L)	404	125-350
Calcium (mmol/L)	2.46	2.15-2.55
Phosphorus (mmol/L)	1.54	1.29-2.26
Magnesium (mmol/L)	0.85	0.75-1.02
Serum creatinine (umol/L)	13.3	25-69
Total Cholesterol (mmol/L)	7.76	<5.18
Albumin (g/L)	22.6	40-55
PTH (pg/ml)	21	15-65
25-Hydroxyvitamin D (ng/ml)	24	>30
C-Reactive Protein (mg/dL)	<0.5	<0.5
Urine Calcium (mmol/L)	1.08	2.5-7.5
Urine Calcium To Creatinine Ratio	0.06	0.05-1.1
24 Hour Urinary Protein (g/24 h)	0.74	<0.4
HIV	Non-reactive	Non-reactive
HBsAg	Non-reactive	Non-reactive
Anti-HCV	Non-reactive	Non-reactive

Note: The urine calcium creatinine clearance ratio was calculated using plasma and 24-hour urine samples for calcium and creatinine.

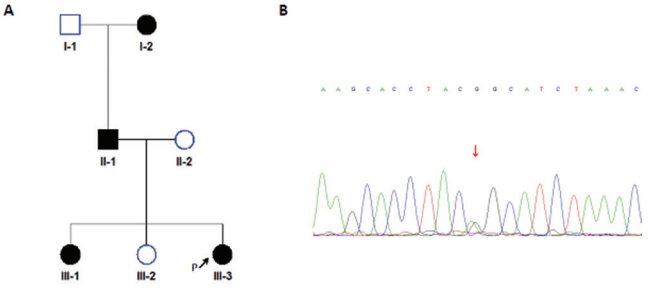
Abbreviations: PTH, parathyroid hormone; HIV, human immunodeficiency virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

Table 2. Calcium Levels of The Family Members

Family Member	Calcium Levels (mmol/L)
Proband	2.95
Grandmother	3.0
Father	2.75
Mother	2.2
Sister 1	3.0
Sister 2	2.81

Note: Calcium levels are presented in millimoles per liter (mmol/L). In this case study, calcium levels are crucial in identifying potential indications of Familial Hypocalciuric Hypercalcemia (FHH), a condition characterized by lifelong hypercalcemia. Elevated calcium levels, as observed in the proband, grandmother, father, sister 1, and sister 2, may suggest the presence of FHH. In individuals affected by FHH, calcium levels remain persistently high, often with reduced urinary calcium excretion, contrasting with other hypercalcemic conditions.

Figure 1. Pedigree and Sanger Sequencing Results of the Family with Familial Hypocalciuric Hypercalcemia (FHH). (A): Black symbols indicate identified variant carriers; open symbols represent individuals without the identified variant. The black arrow points to the proband. (B): Sanger sequencing reveals mutant sequences in the patient. The arrow indicates the position where base substitution results in changes in amino acids.



Note: The figure illustrates the inheritance pattern of the identified variant in the family, highlighting carriers and non-carriers. Sanger sequencing demonstrates the specific genetic mutation in the patient, pinpointing the affected amino acid position.

Clinical Diagnosis of Familial Hypocalciuric Hypercalcemia (FHH). Considering the clinical manifestations, along with normal PTH, elevated blood calcium, and reduced urinary calcium levels, the clinical

diagnosis leaned towards FHH. Subsequently, a genetic analysis was conducted for the family, revealing a missense mutation in the *CASR* gene. Specifically, this mutation resulted in an arginine to glutamine substitution at amino acid 465 in the protein (c.1394G>A, p.R465Q) (Figure 1B), leading to FHH1. The observed phenotypes and genotypes co-segregated, aligning consistently with the clinical diagnosis.

DISCUSSION

NS is a prevalent condition among children, characterized by significant proteinuria, leading to diminished serum albumin levels. Although hypercalcemia is relatively uncommon in NS, there was a notable shift in calcium levels during the follow-up period. It is postulated that hypercalcemia might have been present earlier, particularly when the patient exhibited low albumin levels. During that time, the calcium levels may have appeared 'normal' due to the interaction with low albumin. After the restoration of albumin to normal levels and considering the loss of function in the *CASR* gene, hypercalcemia manifested. It is crucial to note that hypercalcemia in cases of FHH can result in neurodevelopmental retardation, a facet that has historically been overlooked.[13]

In this report, the patient was diagnosed with NS accompanied by mild hypercalcemia. Kidney ultrasonography yielded unremarkable results. A clinical diagnosis of FHH was established and later confirmed through genetic testing, identifying a c.1394 G>A mutation in exon 5 of the *CASR* gene. A robust family history of hypercalcemia was evident, with the grandmother, father, and one sister all exhibiting elevated serum calcium levels. They shared the same mutation. In contrast, another sister (III-2) displayed normal calcium levels, and the mother was normocalcemic. Importantly, none of them presented any symptoms related to hypercalcemia.

All these indications suggest that the *CASR* mutation may manifest with diverse phenotypes. This finding aligns with previous research, demonstrating that both loss-of-function and gain-of-function *CASR* mutations can give rise to FHH and autosomal dominant hypocalcemia, respectively. Additionally, alterations in parathyroid *CASR* expression have been identified as contributing factors to the pathogenesis of primary and secondary hyperparathyroidism.[14]

The *CASR* is a G protein-coupled receptor comprising 1078 amino acids, with high expression observed in the parathyroid gland, kidney, and bone.[15] Notably, this receptor also plays a functional role in various organs, including the stomach, intestinal tract, and cardiovascular system.[14,16,17] The human *CASR* gene is situated on chromosome 3q13.33-21.1 and comprises 7 exons.

CASR engages in cellular responses by activating or inhibiting multiple signaling pathways.[18,19] It plays a crucial role in calcium homeostasis, overseeing PTH secretion and urinary calcium excretion.[20,21] Calcium (Ca^{2+}) serves as a second messenger, playing a pivotal role in fundamental cellular functions such as cell proliferation, activation, and apoptosis.[22]

To date, over 300 *CASR* mutations have been identified in association with FHH, with the majority being missense mutations.[21,23] FHH1 constitutes around 65% of FHH cases.[24] It is an autosomal dominant disorder marked by persistent hypercalcemia, normal or elevated PTH concentrations, and diminished urinary calcium excretion. FHH1 is acknowledged as a rare and benign condition, typically requiring no intervention.[25]

In a study, the reported prevalence of FHH1 was 1.3 cases per 100 000.[26] Ridge et al.,[7] utilizing whole-exome sequencing and clinical laboratory data from a single US health system, identified individuals with FHH1, yielding a higher prevalence of 74.1 per 100 000 for FHH1. The majority of FHH1 patients are asymptomatic. However, some individuals may experience symptoms such as headaches and fatigue, while others may develop complications like acute pancreatitis or chondrocalcinosis.[27,28]

It is crucial to differentiate FHH1 from primary hyperparathyroidism (PHPT). FHH1 is characterized by relatively low urine calcium excretion compared to the increased excretion observed in PHPT.[8] The standard treatment for patients with PHPT typically involves parathyroidectomy. A systematic evaluation of these indicators in individuals affected by FHH1 can prevent unnecessary parathyroid surgery, ensuring appropriate and targeted medical interventions.[29]

In this case, urine calcium was low, and the urine calcium creatinine clearance ratio (CCCR) was 0.06. Previous evidence has suggested that patients with a CCCR < 0.01 should undergo further evaluation on suspicion of FHH.[30] However, a study indicated that a CCCR < 0.01 would accurately classify only 65% of FHH patients.[31] More recently, another study demonstrated that 24% of individuals with FHH had a CCCR above 0.01,[32] aligning with our findings.

This case aims to identify a rare disorder associated with NS. Timely monitoring calcium and other indicators in such cases is crucial to prevent fatal outcomes. By employing plasma calcium and PTH levels, along with the CCCR, in combination with genetic analysis, clinicians can achieve accurate diagnoses, minimizing the risk of misdiagnosis and avoiding unnecessary treatment. However, further investigation is needed to understand the mechanism and function of the *CASR* mutation.

CONCLUSION

In conclusion, this case report sheds light on the uncommon co-occurrence of NS with FHH, emphasizing the rarity of this dual presentation. Through a thorough investigation, we successfully identified a heterozygous mutation in exon 5 of the *CASR* gene within a family affected by FHH. This finding adds to the limited body of knowledge regarding the genetic underpinnings of NS and FHH and underscores the significance of genetic analysis as the gold standard in distinguishing FHH from other potential causes of hypercalcemia. The intricate relationship between these two conditions highlights the complexity of their clinical

manifestations and the importance of a multidisciplinary approach for accurate diagnosis and tailored management. As a rare case exemplar, our report contributes to the broader understanding of the genetic landscape and clinical implications associated with the simultaneous occurrence of NS and FHH, providing valuable insights for clinicians and researchers alike.

CONFLICTS OF INTEREST

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

ACKNOWLEDGMENTS

We thank the patient and family members for their time and effort, as well as the pediatricians.

FUNDING

The work was supported financially by the Effect and Mechanism of Polygonin in Acute Renal Injury in Mice (2018K089B) and the Pediatric Medical Innovation Team of Jiangsu Province (CXTDA2017022).

AUTHOR CONTRIBUTIONS

MY, JH, RW, MW, and YP reviewed the literature and wrote and edited the manuscript. Dr. Gao was the pediatrician managing the patient and reviewed the manuscript. Dr. Xia assisted in reviewing the manuscript and oversaw its preparation. Min Yu and Mei Xue contributed equally to this work.

DATA AVAILABILITY

The data used to support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Informed consent was obtained from the patient's parents to pursue genetic analysis.

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