CASE REPORT

Clinical, Molecular Characterization and Long-Term Follow-Up of a Patient with Neonatal Severe Hyperparathyroidism

Gonçalo Padeira[1], Branca M. Cavaco[2], Daniel Virella[3], Henrique Sá-Couto[4], Maria de Lurdes Afonso-Lopes[1]

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Abstract

Heterozygous inactivating pathogenic variants of the calcium-sensing receptor encoding gene cause autosomal dominant familial hypocalciuric hypercalcemia, whereas mutations that inactivate both alleles cause neonatal severe hyperparathyroidism, a rare and potentially fatal disease. We present the clinical and genetic characterization of a Portuguese family with familial hypocalciuric hypercalcemia/neonatal severe hyperparathyroidism as well as the long-term follow-up of the proband. The newborn was admitted due to progressive hypotonia, feeding refusal, and dehydration. Serum calcium and parathormone levels were markedly increased. Radiological evaluation revealed osteopenia and several fractures. Total parathyroidectomy with the reimplantation of a quarter of one gland was performed. At 15 years old, she is clinically well, has normal calcium levels, and detectable parathormone values while under calcium and α-calcidiol treatment. Calcium-sensing receptor encoding gene sequencing revealed a germline homozygous nonsense pathogenic variant later confirmed as inherited.

Keywords: Genetic Diseases, Inborn; Hypercalcemia/diagnosis; Hypercalcemia/genetics; Hyperparathyroidism/diagnosis; Hyperparathyroidism/genetics; Parathyroid Hormone; Receptors, Calcium-Sensing/genetics; Treatment Outcome

Introduction

The human calcium-sensing receptor (CaSR) plays an essential role in the regulation of extracellular calcium homeostasis. This receptor is found in many tissues throughout the body, but its action is best understood in the parathyroid gland where parathyroid hormone is synthesized and secreted and, in the kidney, where calcium reabsorption and excretion are regulated. Usually, it is activated by elevations in extracellular calcium concentration and promotes normocalcemia by suppressing parathormone (PTH) expression and secretion, promoting renal calcium excretion, and increasing calcitonin secretion.[1,2] The calcium-sensing receptor is a member of the G-protein-coupled receptor superfamily, encoded by six exons of the *CASR* gene, located on chromosome 3q21.1.[3] Structurally, the CaSR comprises a large amino terminal extracellular domain, a classic seven transmembrane domain, and an intracellular carboxy-terminal domain. The CaSR forms disulfide-linked homodimers, which are essential for its activation. The extracellular domain from each monomer, assume a bi-lobed, "Venus-flytrap"-like configuration with a cleft between the lobes. It has been suggested that the binding of calcium to the pocket between the lobes leads to a "Venus-flytrap"-like closure, triggering the transmission of a signal from the extracellular domain to the transmembrane domain, and initiating signal transduction.[4-6]

Heterozygous germline inactivating pathogenic variants in the *CASR* gene can cause familial hypocalciuric hypercalcemia (MIM 145980).[3] When two inactive gene copies are inherited (or one single mutant allele acts in a dominant negative manner), patients may manifest neonatal severe hyperparathyroidism (MIM 239200)[3] presenting life-threatening hypercalcemia in the neonatal period.[7-9] Other related clinical manifestations include bone lesions, feeding difficulties, respiratory distress, and hypotonia.[2] The clinical management of neonatal severe hyperparathyroidism is difficult. Surgical treatment with total parathyroidectomy has been recommended for the most severe cases, but it can lead to iatrogenic hypoparathyroidism. Some

1. Pediatric Endocrinology Unit, Hospital Dona Estefânia, Centro Hospitalar Universitário Lisboa Central, Lisboa, Portugal
2. Molecular Pathobiology Research Unit, Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisboa, Portugal
3. Neonatal Intensive Care Unit, Hospital Dona Estefânia, Centro Hospitalar Universitário Lisboa Central, Lisboa, Portugal
4. Pediatric Surgery Department, Hospital Dona Estefânia, Centro Hospitalar Universitário Lisboa Central, Lisboa, Portugal
Corresponding Author
Gonçalo Luzes Padeira
https://orcid.org/0000-0003-3163-990X
goncalo_padeira@hotmail.com
Hospital Dona Estefânia, Rua Jacinta Marto, 8A, 1169-045 Lisboa, Portugal
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patients benefit from medical interventions (like bisphosphonates and calcimimetics) before surgery or even without surgery.[6] To our knowledge, the long-term follow-up of these patients is scarce.

We present a girl with neonatal severe hyperparathyroidism, born severely hypercalcemic, who had an initial clinical evolution fraught with complications, and her long-term follow-up. We describe the homozygous *CASR* pathogenic variant that was identified in this patient and her family.

Case Report

First daughter of a healthy, young, unrelated couple. The pregnancy and birth were uneventful and the birth weight was adequate. At 7-days-old, she was hospitalized for hypotonia and feeding refusal and, empirical antibiotics were started. The blood cultures and infectious parameters were negative. On the 16th day, she was transferred to neonatal intensive care for severe hypercalcemia.

Upon arrival, she was a sick newborn with hypotonia, respiratory distress, hypoventilation, and a systolic murmur. The laboratory evaluation revealed acidosis, severe hypercalcemia with total calcium 26.9 mg/dL (reference values 8.5-10.1 mg/dL), ionized calcium 3.11 mMol/L (reference values 1.15-1.32 mMol/L), phosphorus 3.1 mg/dL (reference values 3.1-7.7 mg/dL), hypercalciuria with a urinary calcium/creatinine ratio of 3.5 (reference value < 2), and high parathormone (PTH) 1254 pg/mL (reference values 12-65 pg/mL). The long bones radiograph showed marked osteopenia and several greenstick fractures (Fig. 1). The clinical diagnosis of hyperparathyroidism was established. She was started on ventilation support, hyperhydration and furosemide. Despite subjective clinical improvement, hypercalcemia (total calcium > 14.6 mg/dL), and hyperparathyroidism (PTH > 877 pg/mL) persisted.

The cervical ultrasound revealed nodular structures in the posterior aspect of both lobes of the thyroid gland measuring 3-4 mm in diameter but normal size and function of both parathyroids and thyroid were observed on the scintigraphy of the parathyroid with sestamibi (Fig. 1). The renal ultrasound showed hyperechogenic kidneys with nephrocalcinosis.

Severe neonatal primary hyperparathyroidism was presumed and, therefore, molecular studies were conducted.

At 31-days-old, subtotal parathyroidectomy (three glands removed, two cryopreserved) was performed. Histopathologic examination revealed clear cell adenoma. From the 32nd to 45th day, parathormone and calcium decreased, but the attempt to stop hyperhydration and furosemide was unsuccessful, showing that the remaining parathyroid gland was still functioning independently. Therefore, total parathyroidectomy with the reimplantation of one quarter of one gland in the sternocleidomastoid muscle was performed. She was discharged home after nine weeks in hospital.

After the total parathyroidectomy, she developed hypoparathyroidism, which required oral treatment with calcium and α-calcidiol (Fig. 2). Serum parathormone (Fig. 2) remained mensurable, in accordance with a functioning reimplanted parathyroid, allowing for low calcium and α-calcidiol supplements. Frequent adjustments of this therapy were needed to achieve normal plasma levels of total and ionized calcium and parathormone (Fig. 2). By 3 years old, her needs of exogenous calcium had significantly diminished.

The patient is now 15 years old, having achieved adequate growth (Fig. 3). Her height is 158 cm with -0.53 standard deviation score (SDS) within the familial target height, weight 51.8 kg, and a body mass index

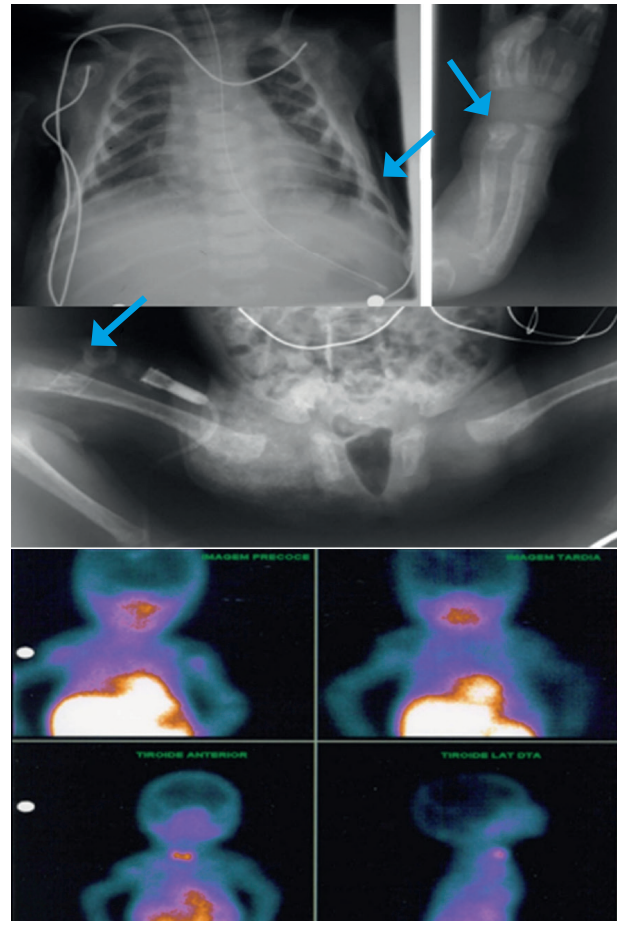


Figure 1. A. Radiographs showing osteopenia and green stick fractures (arrows). B. Scintigraphy of the parathyroid glands (99mTc-sestamibi) and of the thyroid gland (99mTc): Normal size and function of both parathyroids and thyroid.

of 20.75 kg/m^2 (+0.18 SDS). Menarche occurred at 12 years old and she has normal menstrual cycles. Developmental milestones were acquired at normal ages, and she attends school in a grade in accordance with her age.

Bone mineral density in L1-L4, assessed by dual-energy X-ray absorptiometry (DEXA) was 1.087 g/cm^2 (z-score 0.9, within the expected range of variation for age of the peak bone mass).

The pantomography of the teeth and jaw revealed the first molars with anomalous morphology, alteration in the morphology of the crown and presence of only the mesial root, and alveolar resorptive defect of 3.6 (international tooth numbering system) without anomalies in the bone trabeculate (Fig. 4). There is evidence of the regression of nephrocalcinosis.

Molecular studies

Leukocyte deoxyribonucleic acid (DNA) from the proband (III.1) and seven relatives (I.1, I.2, I.3, I.4, II.1, II.2, II.3) (Fig. 5), and 55 healthy unrelated Portuguese controls, was isolated using the standard methods.

The proband was screened for pathogenic variants in the *CASR* gene. Twelve pairs of primers were used for the polymerase chain reaction amplification of exons 2-7, and adjoining splice junctions, of the *CASR* gene. Sequence abnormalities were confirmed by repeat polymerase chain reaction and sequencing.

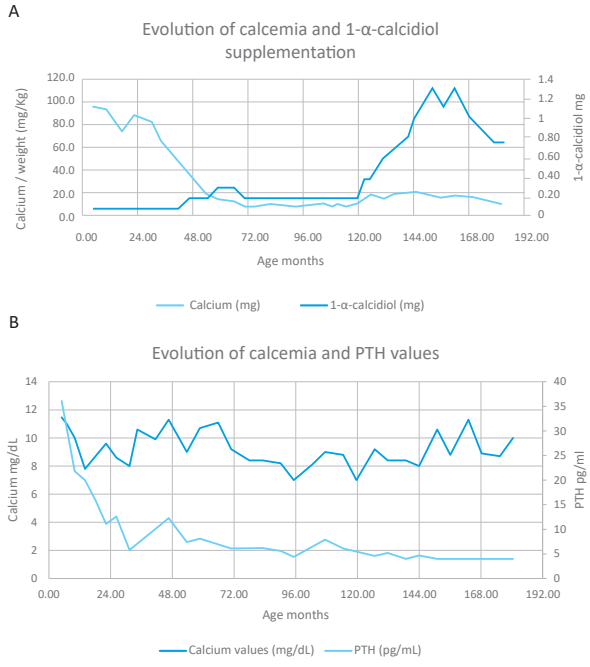
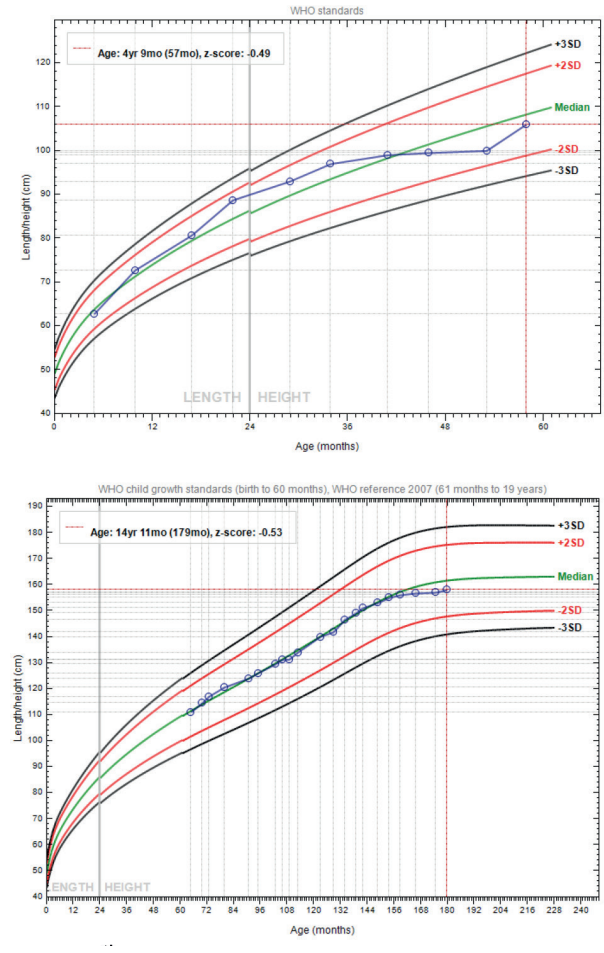


Figure 2. A. Evolution of calcium and 1-α-calcidiol supplementation. Initially, high doses of calcium were required but progressively lower doses were needed. B. Evolution of calcemia and parathormone values showing steady values of calcium and decreasing but always detectable levels of parathormone.

The pathogenic variant identified by direct sequencing in the proband and relatives, was further confirmed by restriction endonuclease analysis with the *Dde*I enzyme (New England Biolabs, Hitchin, Hertfordshire, UK). This approach was also used to confirm the segregation pattern of the pathogenic variant in the family, and to assess its frequency in 55 unrelated Portuguese healthy controls.

Direct DNA sequence analysis of exons 2-7 of the *CASR* gene in the proband, who presented neonatal severe hyperparathyroidism, revealed the presence of a homozygous point mutation, a C>T transition (NM_000388.4:c.679C>T) in the first base of codon 227, resulting in the replacement of CGA (arginine residue) with a TGA (Stop) (NP_000379.3:p.Arg227Ter) (Fig. 5). This mutation is predicted to cause a premature termination of translation in exon 4, which encodes part of the extracellular domain of the CaSR.

Deoxyribonucleic acid sequencing and *Dde*I restriction enzyme analysis disclosed the p.Arg227Ter mutation in the proband parents (II.1 and II.2) and grandfathers



mo - month, yr - year.

Figure 3. Longitudinal growth of the female proband, according to the World Health Organization child growth standards.

(I.1 and I.3), whom were heterozygous for this mutation (Fig. 5). The proband parents had asymptomatic mild hypercalcemia and hypocalciuria. Both grandfathers were asymptomatic, but calcium measurements were not available. Genetic analysis also indicated that the proband's maternal aunt (II.3) and grandmothers (I.2 and I.4) did not carry the mutation.

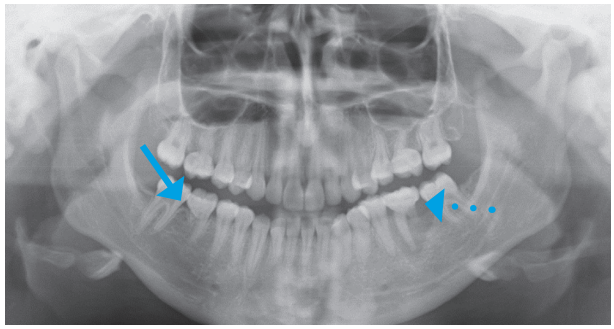
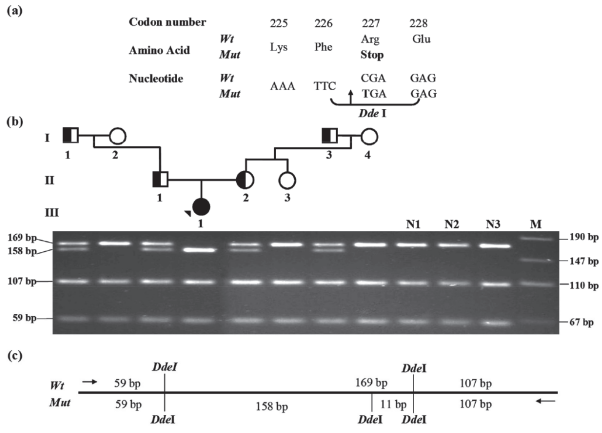


Figure 4. Pantomography of the female proband at 15 years old showing the first molars (solid arrow) with anomalous morphology (alteration in the morphology of the crown and presence of only the mesial root) and alveolar resorptive defect of 3.6 (dotted arrow).



Arg - arginine; Mut - mutant; Wt - wild type sequence.
Squares represent males, circles represent females, open symbols represent unaffected individual, half-filled symbols represent affected with familial hypocalciuric hypercalcemia, full symbols represent affected with neonatal severe hyperparathyroidism, arrow indicates the proband.

Figure 5. Detection of a germline nonsense pathogenic variant in the *CASR* gene in a family with familial hypocalciuric hypercalcemia/ neonatal severe hyperparathyroidism. Deoxyribonucleic acid sequence analysis of the *CASR* gene revealed a homozygous point mutation in the proband (individual III.1), who had neonatal severe hyperparathyroidism. The mutation consisted of a C>T transition in the first base of codon 227, which alters the wild-type sequence, CGA, encoding an arginine to the mutant sequence, TGA, encoding a termination (Stop - Ter) signal (Panel a). The mutation results in the gain of a new *Dde* I restriction endonuclease site (C/TNAG). After the amplification of a 335 bp polymerase chain reaction segment, the cleavage of the mutant sequence with *Dde* I, resulted in four fragments, whereas the wild type sequence generated three fragments. The proband (III.1) was homozygous for the mutant sequence; individuals I.1, I.3, II.1and II.2 were heterozygous, whereas individuals I.2, I.4, II.3 were homozygous for the wild type sequence (panel b). The absence of the C>T transition in 110 alleles of 55 unrelated healthy controls (N1, N2 and N3, shown in panel b) indicated that this was not a common DNA sequence polymorphism.

Discussion

Heterozygous inactivating pathogenic variants in the *CASR* gene cause a decreased sensitivity to extracellular calcium, impairing the ability to sense and correct hypercalcemia, and are the cause of autosomal-dominant familial hypocalciuric hypercalcemia.[2,7-9] Familial hypocalciuric hypercalcemia is characterized by lifelong, mild to moderate but usually asymptomatic hypercalcemia associated with inappropriately low rates of urinary calcium excretion and non-suppressed circulating levels of parathormone, regardless of the presence of hypercalcemia.[2,3] The degree of hypercalcemia in neonatal severe hyperparathyroidism is more severe than that observed in familial hypocalciuric hypercalcemia, due to severe primary hyperparathyroidism.[8,9] Neonatal severe hyperparathyroidism is most commonly associated to the inheritance of two inactive copies of the *CASR* gene.[2,8]

In the present study, we undertook the genetic analysis of a patient with neonatal severe hyperparathyroidism, and identified a homozygous C>T transition, at codon 227 of the *CASR* gene. Calcium binding to a cleft between lobes one and two of the "Venus-flytrap"-like domain causes conformational changes, which are transmitted to the TM domain, thereby leading to receptor activation[4,5,6]. Amino acid residue 227 is located at the "Venus-flytrap"-like domain (lobe 2) in the amino-terminal extracellular domain of the receptor. The present pathogenic variant creates a premature translational stop signal (p.Arg227Ter) and is predicted to cause the loss of normal protein function, either through protein truncation or protein absence (nonsense-mediated messenger ribonucleic acid decay). The absence of this alteration in 110 alleles from Portuguese healthy controls, and in population databases, such as ExAC, supports that it is a pathogenic mutation and not a functionally neutral polymorphism, which would be expected to occur in > 1% of the population.[10]

This pathogenic variant has been previously reported in individuals affected with neonatal severe hyperparathyroidism and familial hypocalciuric hypercalcemia.[11,12] As expected, *in vitro* analysis revealed that the p.Arg227Ter showed no increase in cytosolic free calcium $[Ca^{2+}]_i$ in response to stimulation with extracellular calcium $[Ca^{2+}]_o$.[13]

In conformity with the predicted functional deletion of the human CaSR, the proband had congenital severe neonatal phenotype, which presented soon after birth. The serum calcium and parathormone concentrations

were severely elevated. Skeletal radiographs clearly demonstrated the effects of hyperparathyroidism, including undermineralization of bone, particularly at the extremities, and fractures. All of these features were highly suggestive of neonatal severe hyperparathyroidism.

At the time, early total parathyroidectomy was the treatment of choice for patients with homozygous/compound heterozygous inactivating *CASR* pathogenic variants, as untreated neonatal severe hyperparathyroidism may result in severe neurodevelopmental problems or even death.[2,14] The wide spectrum of severity biochemical and clinical presentation of neonatal severe hyperparathyroidism is usually associated with clinical difficulties in managing a neonate.

In the present case, due to the extreme clinical and biochemical expression of neonatal severe hyperparathyroidism, the decision of performing a parathyroidectomy was taken at the age of 31 days even though the result of the genetic diagnosis was unavailable.[15] Four hyperplastic parathyroid glands were removed, and one quarter of one gland was reimplanted. Recently, the use of cinacalcet is becoming a first line therapy for patients with neonatal severe hyperparathyroidism.[16] Cinacalcet is a positive allosteric modulator of CaSR and increases the sensitivity of the *CASR* on the parathyroid glands, thereby reducing parathormone secretion and serum calcium levels[17] but, at the time (2006), it was not used. There are also reports of patients unresponsive to this therapy, which still must undergo parathyroidectomy to control the disease.[18] Moreover, the proband presented with calcium above 4.5 mMol (18.4 mg/dL), a feature recently described as a biomarker of gravity indicating a homozygous patient and the need of parathyroidectomy to control symptoms.[11,18]

In the early postoperative period, high doses of calcium were required to maintain appropriate serum calcium levels (Fig. 2), probably related to total body calcium deficiency and a shift of large amounts of calcium into undermineralized bone after the correction of severe hyperparathyroidism.[22] Later on (3 years old), the needs of exogenous calcium significantly diminished.

Although she developed iatrogenic hypoparathyroidism, requiring calcium supplementation, the serum parathormone levels remained mensurable and she required lower doses of oral calcium than the standard doses usually necessary for patients with hypoparathyroidism.[19] This probably means that the reimplanted parathyroid gland has remained functional. The tight therapeutic control with combination therapy with calcium and α-calcidiol supplementation probably contributed, in the long term, to the achievement of a longitudinal growth within the familial target height and a normal pubertal development.

The nephrocalcinosis was halted and she is no longer being accompanied by nephrology. The osteodensitometry evaluation has been normal since her second birthday. After the neonatal period, she never had any fractures or other bone problems, reflecting adequate bone mineralization. Nevertheless, she developed short and blunted roots of the first molars, usually seen in patients with hypoparathroidism.[23]

To our knowledge, the adolescent and adult features of neonatal severe hyperparathyroidism have only been reported in a few case reports.[20,21] In these reports, besides the bone metabolism disorder, the main problem has been developing cognitive skills. Most elderly patients have intellectual disability with a lower intelligence quotient, probably resulting from the neonatal hypercalcemia.[21] This is not the case with this patient, probably due to the early diagnosis and tight control.

The p.Arg227Ter pathogenic variant was also detected in the proband parents, and maternal and paternal grandfathers, whom were all heterozygous. The proband parents presented mild hypercalcemia, inappropriate normal levels of parathormone, and low calcium-to-creatinine clearance ratio, as expected in patients with familial hypocalciuric hypercalcemia.[12] Although consanguinity was denied, the rarity of this pathogenic variant, and the fact that both branches of the present family originate from the same Portuguese region, suggest this is likely to be a founder mutation.

In conclusion, we identified a pathogenic variant in the *CASR* gene in a family with familial hypocalciuric hypercalcemia/neonatal severe hyperparathyroidism. We also report the good clinical evolution at a 15 year follow-up of a patient with neonatal severe hyperparathyroidism after early neonatal diagnosis and treatment.

WHAT THIS STUDY ADDS

- Long-term follow-up of a patient with neonatal severe hyperparathyroidism.
- Importance of the early diagnosis and management of hypercalcemia.
- Role of the auto-transplantation of parathyroids.
- Importance of familial hypocalciuric hypercalcemia as a cause of asymptomatic hypercalcemia.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Provenance and peer review

Not commissioned; externally peer reviewed

Consent for publication

Consent for publication was obtained.

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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Caracterização Clínica, Molecular e Seguimento a Longo Prazo de um Doente com Hiperparatiroidismo Neonatal Grave

Resumo

Mutações em heterozigotia inativantes do gene que codifica o recetor sensível ao cálcio são responsáveis pela hipercalcemia hipocalciúrica familiar autossómica dominante, enquanto mutações que inativam ambos os alelos causam hiperparatiroidismo neonatal grave, uma doença rara e potencialmente fatal. Os autores apresentam a caracterização clínica e genética de uma família portuguesa com hipercalcemia hipocalciúrica familiar/hiperparatiroidismo neonatal grave, bem como o seguimento a longo prazo do probando. Recém-nascido internado por hipotonia, recusa alimentar e desidratação. Analiticamente tinha níveis séricos de cálcio e paratormona muito elevados. A avaliação radiológica revelou osteopenia e várias fraturas. Foi realizada paratiroidectomia total com reimplante de um quarto de uma das glândulas. Aos 15 anos encontra-se clinicamente bem sob terapêutica com cálcio e α-calcidiol, com níveis normais séricos de cálcio e valores doseáveis de paratormona. A sequenciação do gene que codifica o recetor sensível ao cálcio detetou uma variante patogénica em homozigotia *nonsense* da linha germinativa posteriormente confirmada como herdada.

Palavras-Chave: Doenças Genéticas Inatas; Hipercalcemia/diagnóstico; Hipercalcemia/genética; Hiperparatiroidismo/diagnóstico; Hiperparatiroidismo/genética; Hormona Paratiroidea; Recetores de Deteção de Cálcio/genética; Resultado do Tratamento