ESPE 2021
The 59th Annual Meeting Online
22-26 September 2021

CLINICAL, MOLECULAR CHARACTERIZATION AND LONG-TERM FOLLOW-UP OF A PATIENT WITH NEONATAL SEVERE HYPERPARATHYROIDISM

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INTRODUCTION

The human calcium-sensing receptor (CASR) plays an essential role in the regulation of extracellular calcium homeostasis. Heterozygous germline inactivating mutations in the *CASR* gene cause a decrease sensitivity to extracellular calcium, impairing the ability to sense and correct hypercalcemia, and have been reported in cases with familial hypocalciuric hypercalcemia (FHH).

When two inactive gene copies are inherited (or one single mutant allele acts in a dominant negative manner), the patients may manifest neonatal severe hyperparathyroidism (NSHPT), presenting life-threatening hypercalcemia in the neonatal period. Other related clinical manifestations include bone lesions, feeding difficulties, respiratory distress and hypotonia.

The clinical management of NSHPT is difficult. Surgical treatment with total parathyroidectomy has been recommended for the most severe cases, but it can lead to iatrogenic hypoparathyroidism.

Some cases benefit from major medical interventions (like bisphosphonates and calcimimetics) before surgery or as an alternative to surgery.

To our knowledge, long-term follow-up of these patients is scarce.

CASE REPORT

First daughter of a healthy, young, unrelated couple. Uneventful pregnancy and birth.
Birth weight: 3100 g (10-25th centile)

16-days-old

Severe hypercalcemia, respiratory distress and hypoventilation
→ Transfer to Neonatal Intensive Care

Analitical evaluation	Value	Reference value
Total calcium	**26,9 mg/dL**	8,5-10,1 mg/dL
Phosphorus	3,1 mg/dL	3,1-7,7 mg/dL
PTH	**1254 pg/mL**	12-65 pg/mL

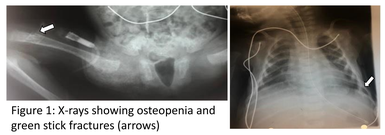

Figure 1: X-rays showing osteopenia and green stick fractures (arrows)

31-days-old

Total parathyroidectomy with reimplantation of ¼ of one gland in the sternocleidomastoid muscle

Hypoparathyroidism
→ Treatment with calcium and *α*-calcidiol

MOLECULAR STUDIES:
CASR gene sequencing
Homozygous nonsense mutation (c.679C>T p.Arg227)

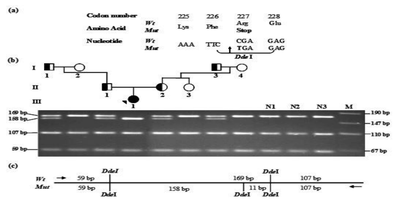

Figure 2: Detection of a germline nonsense mutation in the CASR gene in a family with FHH/NSHPT.

After an initial period fraught with difficulties, meticulous metabolic control of calcium and α-calcidiol allowed for normal growth and development

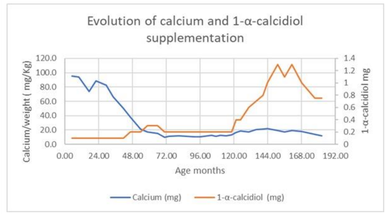

Figure 3: Evolution of calcium and 1-α-calcidiol supplementation.

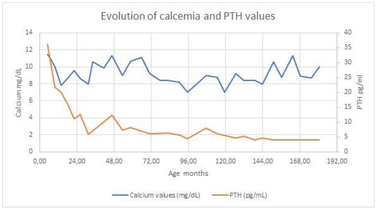

Figure 4:Evolution of calcemia and PTH values showing steady values of calcium and decreasing but always detectable levels of PTH.

15-years-old

- **Height** 158 cm (**-0,53 SDS**; within the familial target height)
- **IMC** 20,75 kg/m² (**+0,18 SDS**)
- **Menarche** 12 years
- **Normal development** and school grade in accordance with age
- **Renal ultrassound** without nephrocalcinosis (previously reported)
- **Bone mineral density** in L1-L4 (DEXA) 1,087g/cm² (z-score 0,9)
- **Pantomography** of teeth and jaw: first molars with **anomalous morphology**

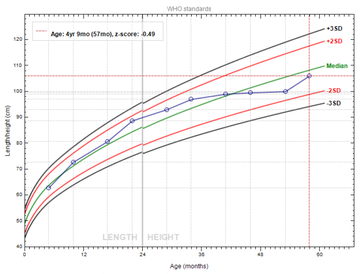

Figure 5: Longitudinal growth of the female proband, according to WHO child growth standards.

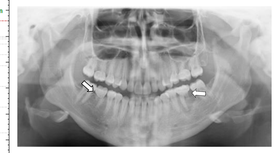

Figure 6: Pantomography showing first molars (solid arrow) with anomalous morphology (associated with hyperparathyroidism).

CONCLUSIONS

In this girl, a mutation in the CASR gene was identified in a family with FHH/NSHPT.

The complexity of this clinical condition requires a multidisciplinary approach to minimize morbidity. In the present case, total parathyroidectomy with reimplantation was needed to control hypercalcaemia. After a challenging admission to control calcium levels, a good clinical evolution was reported at fifteen-year follow-up.

Identification of a CASR mutation allowed family genetic counseling.

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ACKNOWLEDGEMENTS

We are thankful to the family for the consent to report the case.

This case-study was supported by IPOLFG and Associação de Endocrinologia Oncológica, Lisboa, Portugal

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