

Authors: **Gilda Belli¹, Cecconi Antonella², Romano Silvia², Daniele Ciofi¹, Stefano Stagi^{1,3}**

¹ Department of Health Science, University of Florence, Anna Meyer Children's University Hospital, Florence, Italy

² Pediatrics Medical Genetics, Hospital S. Maria Annunziata Bagno a Ripoli, Florence, Italy.

³ Division of Pediatric Endocrinology, Anna Meyer Children's University Hospital, Florence, Italy

BACKGROUND

Neonatal hypocalcemia is a common disorder, occurring more often in premature, low birth weight and asphyxiated infants, as well as in infants born to mothers with diabetes. Nevertheless its aetiology is heterogeneous ranging from iatrogenic, idiopathic and inherited metabolic abnormalities (Figure1). Among these, **Autosomal Dominant Hypocalcemia (ADH, OMIM #601198)** is a rare syndrome characterized by the presence of inappropriately low concentration of circulating parathyroid hormone (PTH) with varying entity of hypocalcemia, high serum phosphate and relatively high urinary calcium excretion, due to an activating mutation in calcium -sensing receptor (CaSR).

CASE REPORT

A female infant was born at 36 weeks of gestational age, IA 8-10, birth weight 2,560 Kg, from a pregnancy complicated by gestational diabetes treated with insulin. Laboratory examinations at birth showed hypoglycemia, **hypocalcemia, high serum phosphate**: proposita showed also cerebral calcifications at brain ultrasound. For the persistence of hypocalcemia and high serum phosphate, in association with very **low levels of PTH**, she was referred at 7 months of age to our Department for a suspected disorder of calcium metabolism. Her family history was positive for a **maternal heterozygous mutation in CaSR** which required oral supplementation with calcium and vitamin D; mother's dual X-ray absorptiometry was normal but calcaneus ultrasound showed poor bone quality. On admission, total calcium, ionized calcium (iCa), phosphate, were respectively 2.1 mmol/L (2.12-2.62 mmol/L), 0.95 mmol/L (1.07-1.32 mmol/L), 2.71 mmol/L (1.55-2.71 mmol/L); PTH was below the reference range (<3 ng/L; 12-72 ng/L) while alkaline phosphatase and 25(OH)vitamin D were normal. An abdominal ultrasound showed **hyperechoic renal spots suggestive for mild nephrocalcinosis** (Figure2). Indeed, genetical analysis revealed a **heterozygous single missense mutation S820F in exon 7 of the CASR gene** (as her mother). Therefore, she started **supplementation with calcium carbonate (320 mg a day) and vitamin D (400 UI)**. At 9 months of life, laboratory investigations revealed normal values of serum total calcium (2.12 mmol/L) and phosphate (2.58 mmol/L) despite ionized calcium (iCa) was persistent low (0.92 mmol/L) as well as PTH (8.96 ng/L).

Table 1 Main diseases related to CaSR anomalies

Hypocalciuric hypercalcaemia syndromes:

- Genetic via inactivating mutations of the *CASR* gene
 - o heterozygous (familial benign hypercalcaemia), NB: Serum calcium levels of the variants A986S, R990G and Q1011E slightly higher than in the general population
 - o homozygous, compound heterozygous (severe neonatal hyperparathyroidism)
- Acquired via anti-CaSR blocking antibodies (rare)

Hypercalciuric hypocalcaemia syndrome, more rare,

- Genetic via heterozygous activating mutations of the *CASR* gene
 - o autosomal dominant
 - o sometimes with presentation of pseudo-Bartter's syndrome
- Acquired via anti-CaSR stimulating antibodies

Other disorders

- Hypercalciuria - lithiases R990G variant of CaSR
- Cancers: tumor suppressor or oncogenic (colon, breast, prostate, neuroblastoma, etc.)
- Metabolic syndrome
- Hypergastrinaemia
- Inflammatory digestive and respiratory diseases
- Taste (kokumi)

Figure 1. Vahe C et al. **Diseases associated with calcium-sensing receptor**. *Orphanet J Rare Dis*. 2017



Figure 2. *Hyperechoic renal spots suggestive for mild nephrocalcinosis*

	Before diagnosis (7 months of life)	After diagnosis (9 months of life)
Total serum calcium (2.12-2.62 mmol/L)	2.1 mmol/L	2.12 mmol/L
Ionized calcium (iCa) (1.07-1.32 mmol/L)	0.95 mmol/L	0.92 mmol/L
Phosphate (1.55-2.71 mmol/L)	2.71 mmol/L	2.58 mmol/L
PTH (12-72 ng/L)	<3 ng/L	8.96 ng/L

CONCLUSIONS

ADH is a rare entity, however, it should be considered in the differential diagnosis of neonatal hypocalcemia. Moreover, diet plays an important role since at the moment of weaning the oral calcium intake decreased, possibly worsening hypocalcemia. Because of its rarity and its varying clinical presentation, a strict monitoring of the calcium balance is required together with a tailored adaptation of the dosing of supplementation to each single patient.

References

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