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

Novel single nucleotide variation in DUOX2 and NPTX1 genes in two Sardinian sisters with transient congenital hypothyroidism

A. Ibba[1], C. Guzzetti[1], L. Casula[1], A. Murianni[1], L. Persani[2], S. Loche[1]

[1]S.S.D. Endocrinologia Pediatrica e Centro Screening Neonatale, Ospedale Pediatrico Microcitemico "A. Cao", ARNAS. Brotzu, Cagliari, Italy

[2]U.O. Endocrinologia e Malattie del Metabolismo - Auxologico San Luca, Milano, Italy

ARNAS "G. Brotzu"

INTRODUCTION

Transient congenital hypothyroidism (TCH) refers to a temporary deficiency of thyroid hormone identified after birth, with low thyroxine (T4) and elevated thyrotropin (TSH). Approximately 17%-40% of children diagnosed with CH by newborn screening (NBS), have transient hypothyroidism. Causes of TCH are prematurity, iodine deficiency, maternal thyrotropin receptor blocking antibodies, maternal intake of anti-thyroid drugs, maternal or neonatal iodine exposure, hepatic hemangiomas and genetics. The classic clinical symptoms and signs of CH are usually absent immediately after birth in the vast majority of infants due to temporary protection from maternal thyroxine. NBS has been largely successful in preventing intellectual disability by early detection of CH by performing thyroid function tests in infants with abnormal screening results. Levo-thyroxine (L-T4) early treatment is recommended at the dose 10-15 µg/kg/day. Children with thyroid gland *in situ* should be re-evaluated after the age of 3 in order to differentiate a transient from a permanent form. Several genetic variants, including *dual oxidase 2* (DUOX2), have been described in patients with TCH.

DUOX2 (15q15.3) encodes for a glycoprotein member of the NADPH oxidase family required for iodine organification and thyroid hormone synthesis.

NPTX1 (Neuronal Pentraxin 1, 17q25.3) is exclusively localized to the nervous system, and probably regulates neural lineage specification from pluripotent stem cells. To date, no association has been reported between NPTX1 and CH.

CASE REPORT

Two sisters (C.M. and I.M.) born in 2013 and 2017 from uneventful pregnancies. Prenatal, neonatal medical history were unremarkable. No consanguinity, no other family members affected. CH has diagnosed by NBS. Serum thyroglobulin was on reference range and the thyroid ultrasound showed a thyroid gland *in situ* without abnormalities. Thyroid scintigraphy was not performed. Both sisters required small doses of L-T4 (≈2 µg/kg/day) to maintain normal serum fT4 and TSH in the first 3 years of life. Growth rate according to age was adequate. Neurological, cardiological, ophthalmological, and audiological evaluation and abdominal ultrasound were negative. Next generation sequencing revealed a homozygous *DUOX2* missense variant p.A297S (c-G889T) in exon 8 (rs 755241413, MAF<0.01), and a heterozygous *NPTX1* missense variant p.L95V (c.C283G) in exon 1, (rs 371219313, MAF<0.01).

After withdrawal from therapy both sisters have occasionally presented slightly elevated serum TSH (<10 µUI/ml) with normal fT4.

	Screening DBS			Screening serum		1 year		2 year		3 year		5year		6 year	
	TSH (nv <6)	fT4 (nv >6)	Thyroglobulin	TSH µUI/ml	fT4 ng/dl	TSH	fT4	TSH	fT4	TSH	fT4	TSH	fT4	TSH	fT4
CM	131	6.6	46.8	150	3.12	0.43 (0.02-1.0)	1.43 (1.3-1.62)	1.54 (1.27-1.82)	0.89 (0.29-1.5)	6.54 (4.1-9.68)	1.27 (1.18-1.37)	6.17 (5.52-8.58)	1.63 (1.36-1.69)	6.96 (6.1-7.8)	1.5 (1.38-1.73)
IM	45.8	13.3	/	150	0.42	2.44 (1.35-4.8)	1.48 (1.3-1.55)	6.62 (2.15-14.08)	1.62 (1.4-1.71)	3.2 (3.1-9.95)	1.34 (1.29-1.46)	/	/	/	/

Thyroid hormones values of the two sisters over the years. Both stopped the therapy at the age of 3 years. Reference value for TSH: 0.64-6.27 µUI/ml, and fT4: 0.78-1.76 ng/dl. Values are expressed as median and IR.

CONCLUSIONS

Novel missense variants of DUOX2 gene and NPTX1 gene were found in two sisters with CH. It is not clear if the DUOX2 variant found in these patients is associated with persistent slightly elevated serum TSH and if it will progress to hypothyroidism and eventually will require hormone replacement in the long term follow-up.

While DUOX2 variants are known to be associated with TCH, the significance of the NPTX1 variant and its pathogenic activity are not known and need further investigation.

REFERENCES

•**Bosch i Ara L. et al.** Congenital Hypopituitarism During the Neonatal Period: Epidemiology, Pathogenesis, Therapeutic Options, and Outcome. Front Pediatr 2021;8:600962.

•**Gregory LC, Dattani MT.** The Molecular Basis of Congenital Hypopituitarism and Related Disorders. The Journal of Clinical Endocrinology & Metabolism 2020;105(6):e2103–20.

•**Boles NC, et al**. NPTX1 Regulates Neural Lineage Specification from Human Pluripotent Stem Cells. Cell Reports 2014;6(4):724–36.

CONTACT INFORMATION

Dr Anastasia Ibba
+39 07052967904/7905
anastasia.ibba@aob.it
endocrinologia.pediatrica@aob.it