TBG deficiency and Central Congenital Hypothyroidism (CH-C): Our experience in neonatal screening with TSH and T4

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The new 2020 ESPE guidelines on congenital hypothyroidism (CH) include detection of CH-C in screening programs. CH-C must be distinguished from T4-binding globulin (TBG) deficiency. It is important to determine whether thyroid function tests reliably separate CH-C from TBG deficiency. TBG (*blood thyroxine transporter globulin*) deficiencies, which is common in the population and does not carry a risk of mental retardation.

Objective

Analyze CCH detection program results from 3 Autonomous Communities (AC) of Spain, at our Public Health Regulatory Laboratory (LNSP):

- TSH and total T4 (TT4) in dried blood spot (DBS) at initial screening (48 hours of life) and at retesting.
- Describe the characteristics of neonates with screening compatible with CCH.
- Consider whether TBG deficiency (TBGD) is an added difficulty in said study.

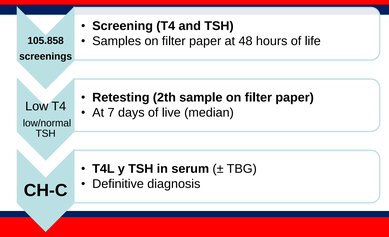
Material and methods

Retrospective study (May 2016-May 2020) of all neonates ≥33 weeks and/or ≥1500 grams referred to the Child Endocrinology services of 3 AC from the LNSP due to low T4 (<6 µg/dL), out of a total of 105,858 CH screenings.

The positives for low T4 (<6 µg/dL) in the retesting compatible with CCH (low T4 and low/normal TSH) were analyzed. After determination in serum, the diagnoses were:

1. CCH: low free T4 (FT4) and low/normal TSH
2. TBG deficiency (TBGD): normal FT4 and TSH
3. Hyperthyrotropinemia: normal FT4 and elevated TSH
4. Euthyroid sick syndrome.

Clinical and laboratory variables were compared between CCH and TBGD. The evolution of the cases considered CCH was assessed.



Results

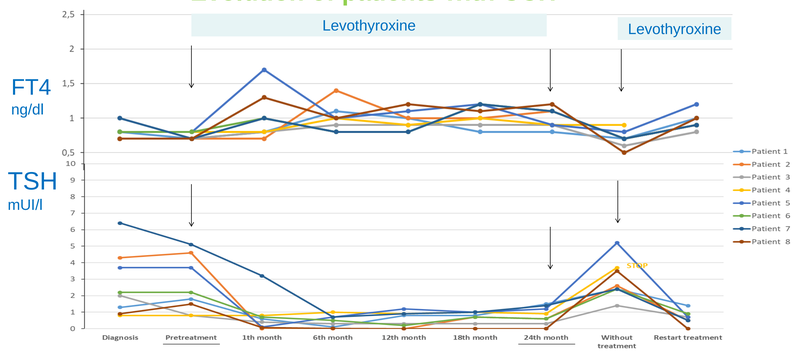
Forty-four neonates were referred due to low TT4, 15 corresponding to primary CH and 29 cases were compatible with CCH.

The final diagnosis of the positives with initial suspicion of CCH was: 15 TBGD, 8 CCH, 5 hyperthyrotropinemia and 1 euthyroid sick syndrome. CCH prevalence in this period was 1/13,333 screenings.

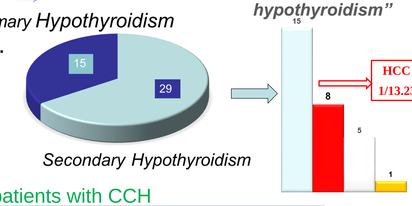
*U Mann-Whitney	CCH (mean ± DE) n=8	TBGD (mean ± DE) n=15	
Gestational age (weeks)	38,7 ± 1,9	38,3 ± 2,0	ns
SDS-weight at birth	0,4 ± 0,9	-0,3 ± 1,0	ns
SDS-Lenght at birth	0,5 ± 0,4	-0,4 ± 1,1	ns
TSH screening (mIU/L)	1,8 ± 0,2	1,9 ± 0,9	ns
TT4 screening (mcg/dL)	2,2 ± 0,2	4,4 ± 0,9	0.000*
TSH retesting (mIU/L)	2,0 ± 0,0	1,9 ± 0,2	ns
TT4 retesting (mcg/dL)	2,3 ± 1,4	3,7 ± 1,3	0.034*
TSH serum (mIU/L)	2,8 ± 1,8	3,8 ± 0,9	ns
FT4 (ng/dL)	0,7 ± 0,1	1,5 ± 0,4	0.000*

Statistically significant differences were found in FT4 values when comparing CCH and TBGD.

Evolution of patients with CCH



SCREENING WITH LOW T4:



Genetic analysis of the patients with CCH

	MRI HPT-HPF	GENETICS
Patient 1	NORMAL	CCDC59 p.G26R 0.7-1.2%
Patient 2	pituitary hypoplasia	GATA2 p.P161A 03% / ZNHX3 p.N1025S n.d.
Patient 3	NORMAL	GATA2 P.p161a 0,3% / ZFHX3 inframe deletion
Patient 4	NORMAL	in process
patient 5	pituitary hipoplasia	IGSF1 p.M1076I 0,49% / DROSHA p.P56S 0,68%
Patient 6	pituitary hypoplasia	in process
Patient 7	NORMAL	
Patient 8	NORMAL	Not done

All CCH started treatment with levothyroxine with a median age of 9.5 days (7-155). 1 patient with multiple hormonal deficiency and 7 patients with isolated CCHs have been diagnosed (according to evolution data and/or genetic results). 6 out of 8 patients with CCH also had TBGD.

Conclusions

-The determination of TT4 in neonatal screening has diagnosed 8 patients with CCH.
-TBG defect is very common in the population; TBGD diagnosis does not exclude a CCH, since they can coexist.
- Genetic studies would help to confirm CCH diagnosis

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