Neonatal screening program for Central Congenital Hypothyroidism

D. Braslavsky, L. Prieto, A. Keselman, L. Gruñeiro Papendieck, R. Enacan, V. Méndez, I. Bergadá, A. Chiesa.

Centro de Investigaciones Endocrinológicas "Dr. César Bergadá" (CEDIE) CONICET–FEI–División de Endocrinología, Hospital de Niños "Ricardo Gutiérrez" Buenos Aires, Argentina

Background

Congenital hypothyroidism (CH) is a heterogeneous entity that includes hypothalamo-hypophyseal system disorders: *Combined pituitary hormone deficiency (CPHD), TRH-R defects, β-TSH deficiency and IGSF1 mutations.* Newborns with **CH of central origin (CH-C)** are missed on TSH based screening programs. Additional T4 determination might help to early detect CH-C leading to reduce morbidity and mortality from CPHD which represents ~ 75% of all CH-C.

Aim

To conduct a neonatal screening based on TSH and T4 determinations for early detection of CH-C.

Population & Methods

37045 term newborns aged 2-7 days were screened.
From June 2014 to June 2015
TSH (IFMA Delfia); cutoff 10 mU/L &
T4 (FIA Delfia); cutoff 4.5 ug/dL (-2.3 SDS)
measured in filter paper blood samples

positive for CH-C

- **Clinical Assessment**
- **Biochemical Assessment**
- **Brain & Thyroid US**

- **Serum TSH, T4, FT4, T3, Thyroglobulin, Antithyroid-ab**
- **TBG** (in patients likely to have hypoTBGemia)
- **Cortisol, GH, prolactin, LH/FSH, Testosterone (boys)**
- **Glycemia, electrolytes**

Results

TSH >10 mU/L	Low-normal T4	Primary hypothyroidism (n=23)
TSH ≤10 mU/L	Normal T4	Normal (n=36998)
	Low T4	Central hypothyroidism (n=24)

Confirmation stage

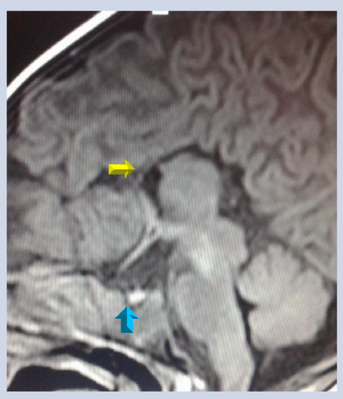
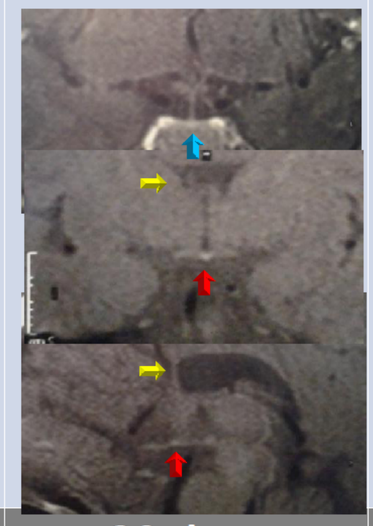
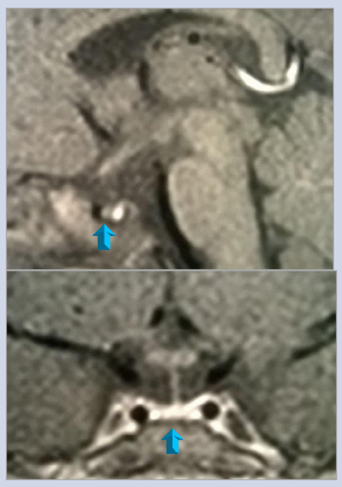
- **Permanent CH-C (n=3)** — Prevalence 1:12348
- **HypoTBGemia (n=5)**
- **Transient hypoT4 (n=16)**
  - Non thyroidal illness (15)
    - In patients (13) (respiratory distress, sepsis)
    - Urinary tract infection (1)
    - Isolated ACTH deficiency (1)
  - Healthy (1)

Laboratory determinations

	Paper filter		Serum samples						
	T4 ug/dL	TSH mU/L	T4 ug/dl Mean (±SD)	FT4 ng/dL Mean (±SD)	T3 ng/dL Mean (±SD)	TSH mU/L Mean (±SD)	Tg ng/dL Mean (±SD)	Thyroid Ab	TBG ug/dl
CH-C	3.9	<2.0	3.7 (1.5)	0.61 (0.14)	33.6 (31.3)	4.29 (2.57)	34.7 (29.8)	negative	NA
HypoTBG	2.6	<2.0	2.3 (0.5)	1.37 (0.32)	57.7 (10.2)	2.96 (0.76)	19.0 (10.3)	negative	<3.5
Transient hypoT4	3.9	<2.0	10.9 (2.8)	1.65 (0.47)	151.8 (68.0)	4.20 (1.9)	55.8 (36.3)	negative	NA
Normal range	<4.5	2.0-10	6-18	1.0-2.6	80-260	1.3-10	18-145		15-40

Tg: Thyroglobulin; Thyroid Ab: antithyroid-antibodies; TBG: Thyroid binding globulin; NA: not available.

Combined Pituitary Hormone Deficiency

	Case I	Case II	Case III
Gender	Boy	Boy	Girl
Hormone Deficiencies	ACTH, TSH, ADH	ACTH, TSH	GH, TSH, PRL
MRI			
Hormone replacement	8 days	20 days	9 days
Sequenced genes*	*LHX4 +/+ HESX1 +/+*	*LHX4 +/+ HESX1 +/+*	*POU1F1 +/- R271W, de novo*

Corpus callosum hypoplasia/ Absent septum pellucidum

Anterior pituitary hypoplasia

Ectopic neurohypophysis

Conclusions

T4 determination allows the identification of CH-C as a prevalent condition.

Diagnosis of CH-C helps to early identify CPHD preventing mayor morbidity and mortality.

This screening strategy requires experienced specialists to ***confirm the diagnosis of CH-C*** as well as to rule out transient low T4 disorders.

The elevated prevalence of CH-C highlights the importance of evaluating its cost-effectiveness in current neonatal screening programs.

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Aix-Marseille Université, Hôpital Conception & Hôpital Timone, Marseille, France.

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