Congenital Hypothyroidism: neonatal screening program with T4 and TSH

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INTRODUCTION

• Most congenital hypothyroidism screening programs use TSH as the method, to detect it. In this situation, the congenital central hypothyroidism represents a major false negative result of the reflex TSH strategy.
• If the screening program uses TSH and T4, cases of central congenital hypothyroidism can be diagnosed.
• Since May 2016, in our Community, neonatal screening for congenital hypothyroidism has been performed by determining total TSH and T4 on filter paper.
• The prevalence of congenital hypothyroidism is estimated between 1/16 000 and 1/100 000; such variable prevalence probably depends upon several factors including ethnicity but also differences in sensitivity of the diagnostic strategies.

OBJECTIVES

• To determine children diagnosed with central congenital hypothyroidism by a screening program using TSH and total T4 between May 2016 and January 2019.
•To analyze the characteristics of the disease in these children.

MATERIAL AND METHODS

• During the time of the study, 14.743 newborns have been screened.
• Cut-off points are used for TSH ≥10 mU/ml and T4, 6 and 20 mg/dl as lower and upper limits.
• When the result was positive, a second sample was performed on filter paper and if the second sample was also positive, the patient was sent to the Pediatric Endocrinology Unit to confirm the results.
• Diagnosed of congenital central hypothyroidism was made with the combination of low FT4 and inappropriate low TSH. If the patient was diagnosed with congenital central hypothyroidism, hormonal studies, skull MRI and genetic analyses were performed.

RESULTS

For total T4 values, first simple screening was positive (T4<6 or >20 mg/dl) in 112 patients (0.76% of total). Of these cases, the second sample continued to be positive in 17 cases (0.11% of the total), in which 10 the diagnosis was confirmed. There were 2 cases with alterations of total T4 above the limit due to partial resistance to thyroid hormones. The other 8 cases, had total T4 below the limit, being 2 hipothyroxinemias of the prematurity and 6 central congenital hypothyroidism.

Screening results

	Newborn screened	Congenital hypothiroidism confirmed/Central congenital hypothiroidism
May -Dec 2016	3.762	3/1
Jan –Dec 2017	5.654	3/2
Jan –Dec 2018	5.326	6/3

	1st screening positive	2nd screening positive
TSH	1’5±0,61 mU/l	2.44±1,36 mU/l
T4	T4: 1’89±0,25 ug/dl	0’79±0,07 ng/dl

The incidence rate was 0,4 /1000 children participating in the screening (1/2500)
There were 6 cases diagnosed of central congenital hypothyroidism (from May 2016 to Dec 2018), and all were male.

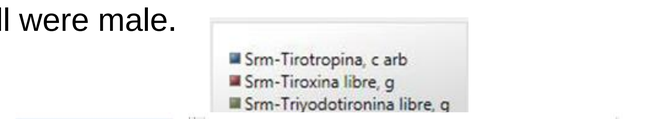
Levels of thyroid hormones at diagnosed

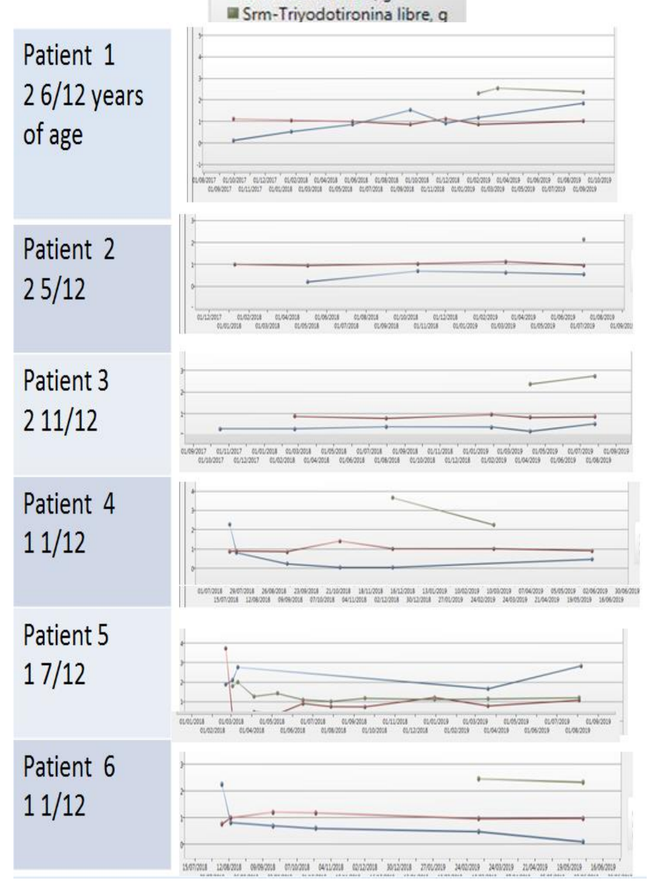
Patient	1	2	3	4	5	6
screening						
TSH mU/l NV <10	0.83	1,84	1.5	2	1.7	2
T4 ng/dl N.V 6-20	2,57	2.1	2.8	1.1	1.9	1.8
re-evaluation						
TSH mU/l N.V 1.1-6.3	1.3	4,3	2.05/0.78	2.25	3.7	2.24
FT4 ng/dl N.V 0.8-1.8	0.82/074	0,71	0.73/0.74 4 months	0,84	0.88	0.74
FT3 ng/dl N.V 2.1-4.2	1.97	1,73	2.1/2.56	2.1	1.86	2.1
TSH index N.V 2.7±0.6	1.39	1.85	1.55	1.80	2.08	1.61

the study of the pituitary hormones have been normal in all patients, and the MRI of the skull showed hypoplasic adenohypophysis in 3 cases.
Genetic analysis of all genes known to be involved in central congenital hypothyroidism (IGSF1, TRHR, TSHB, TBLX1..) are under investigation, with some positive results.

Results of complementary tests and evolution

Patient age	Doses l-tiroxin mcg/k/d	MRI	Genetic analysis/VARIANT/ MAF	H-H hormones FSH UI/l LH UI/L ACTH ng/l Cortisol ug/dl Prolactin ug/l
Patient 1 2 6/12 years	7.5 to 2.2	Normal	No results yet	0.84 1.28 24,9 2.3 82
Patient 2 2 5/12 years	10 to 2.6	hypoplasic adenohypo-physis	GATA2 p.P161A 03% ZNHX3 p.N1025S nd	0.3 3.1 23.9 1.3 125
Patient 3 2 11/12 years	3.5 to 2.7	Normal	ZFHX3 inframe deletion ZFHX3 inframe deletion	N
Patient 4 1 1/12 years	6.4 to 3.2	Normal	On going	9.5 10 103 0,3 148
Patient 5 1 7/12 years	7,3 to 3.5	hypoplasic adenohypo-physis	IGSF1 p.M1076I 0.49% DROSHA p.P56S 0.68%	2.8 2.2 33.8 2.6
Patient 6 1 1/12 years	6.8 to 3.7	hypoplasic adenohypo-physis	On going	1.4 2.2 13 11 33





None of them had symptoms of hypothyroidism at diagnosis.
Treatment was initiated with a medium age of 9’4±1,82 days (except one case with 5 months) with L-thyroxin at a medium dose of 7 mcg/K/d.
At present, all continue treatment at a medium dose of 3 mcg/kg/day. None of the patients have had hyperthyroidism during treatment.

CONCLUSIONS

1. The analysis of TSH and total T4 in neonatal screening makes it more accurate the diagnosis of thyroid disfunction.
2. Congenital central hypothyroidism represents a challenging condition in clinical practice
3. The prevalence of congenital central hypothyroidism in our community is high, not being able to know the cause, although the genetic study can help with the diagnosis.

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