Early determinants of thyroid function outcome in children with congenital hypothyroidism and a normally located thyroid gland: a regional cohort study

C Saba, S Guilmin-Crepon, D Zénaty, L Martinerie, A Paulsen, D Simon, S Dos Santos, J Haignere, D Mohamed, JC Carel, J Léger

Assistance Publique-Hôpitaux de Paris, Robert Debré University Hospital, Pediatric Endocrinology Diabetology Department and Unit of Clinical Epidemiology, Paris Diderot University, Inserm 1141 and CIC-EC 1426, Reference Centre for Endocrine Growth and Development Diseases, F-75019 Paris, France.

BACKGROUND

·An increase in the incidence of congenital hypothyroidism (CH) with a normally located gland has been reported worldwide.
We recently demonstrated, in a nationwide study in France, that the increase in the incidence of CH with a eutopic gland includes not only mild cases, but also more severe CH phenotypes, suggesting that shifts in diagnostic criteria, with a decrease in TSH cutoff from 30 to 20 mIU/l, were not the only reason for the observed increase in incidence.
(Barry Y et al. Annals of epidemiology 2016)

·Affected individuals display transient or permanent CH during follow-up in childhood. According to current guidelines, children with CH and a normally located gland should undergo a re-evaluation of thyroid function at or before the age of three years, to distinguish between cases of transient and permanent CH.

AIM OF THE STUDY

In this regional cohort study, we investigated the current prevalence of transient hypothyroidism in patients initially treated for CH with a eutopic gland, with the aim of identifying clinical characteristics that can be used for the very early prediction of outcome.

PATIENTS AND METHODS

This observational cohort study included all patients identified by systematic neonatal screening for CH in the northern Parisian region between 2002 and 2012 and treated for CH with a normally sited gland.
A standardized data collection form was completed prospectively at diagnosis.
Patients were classified, during the follow-up, as having transient or permanent CH.

In total, 92 patients treated for CH with a normally located gland were included in the study.
Patients were a median (25^{th}-75^{th} percentile) of 19 (10-25) days old at treatment initiation, with median TSH and FT4 concentrations of 69 (35-230) mIU/l and 12.8 (7.3-15.7) pmol/l, respectively. The median initial dose of LT4 was 8.4 (6.5-10.0) µg/k/d.

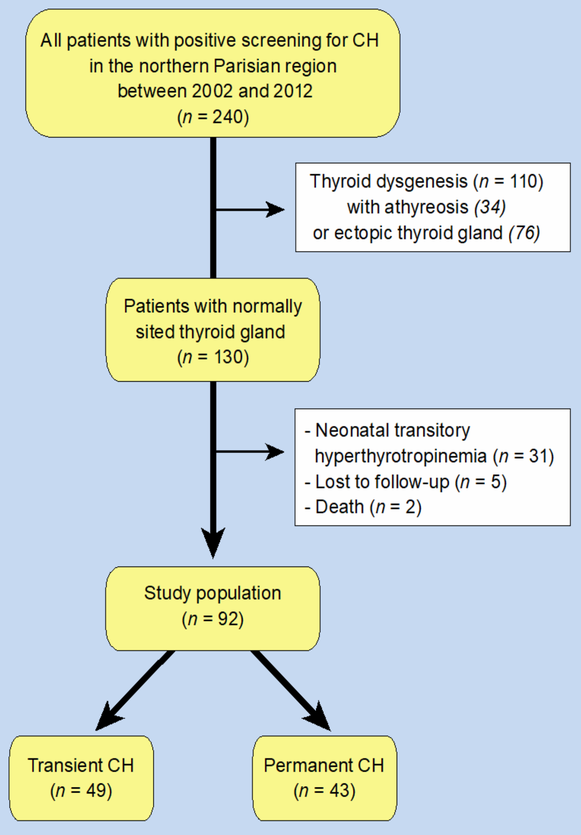

Figure 1 Flow chart of the study

RESULTS

Of the 92 patients initially treated for CH with a normally located gland during the neonatal period, **49 (54%) had a transient form of CH** after the cessation of levothyroxine treatment at 1.5 (0.6 - 3.2) years of age.

Table I: Clinical characteristics of patients with transient and permanent forms of CH with a normally located gland

	Transient *n* = 49	Permanent *n* = 43
Sex		
Male	26 (53%)	22 (51%)
Female	23 (47%)	21 (49%)
Prematurity		
yes	8 (17%)	9 (22%)
no	39 (83%)	32 (78%)
Birth weight SDS	-0.36 (-1.76; 0.65)	-0.14 (-0.61; 0.71)
Birth length SDS	-0.60 (-1.23; 0.04)	-0.26 (-0.88; 0.58)
Small for gestational age		
yes	13 (28%)	5 (12%)
no	34 (72%)	36 (88%)
Any neonatal problems (premature, SGA and/or neonatal distress)		
yes	13 (27%)	15 (35%)
no	36 (73%)	28 (65%)
Associated malformations or dysmorphic features		
yes	7 (14%)	12 (28%)
no	42 (86%)	31 (72%)
Iodine overload		
yes	10 (20%)	4 (9%)
no	39 (80%)	39 (91%)
Ethnicity		
Caucasian	14 (47%)	13 (50%)
Non-Caucasian	16 (53%)	13 (50%)
Familial congenital hypothyroidism		
yes	1 (2%)	8 (20%)[c]
no	48 (98%)	33 (80%)
Consanguinity		
yes	2 (9%)	11 (46%)[c]
no	21 (91%)	13 (54%)
Age at diagnosis (d)	20 (12; 24)	11 (8; 21)[c]
Serum TSH at diagnosis (mIU/l)	49 (23; 89)	142 (57; 366)[d]
FT4 at diagnosis (pmol/l)	12.8 (10.3; 15.2)	11.8 (4.9; 16.0)
FT4 at diagnosis (pmol/l) (3 classes)		
<5	4 (9%)	10 (25%)
5-9.9	6 (13%)	8 (20%)
≥ 10	35 (78%)	22 (55%)
Bone maturation at diagnosis (knee epiphyseal ossification centers)		
at least one present	38 (83%)	35 (88%)
both absent	8 (17%)	5 (13%)
Thyroid volume on ultrasound scan		
normal	34 (72%)	22 (54%)
hypoplastic/hemithyroid	0/2 (4%)	3/3 (14%)
goiter	11 (23%)	13 (32%)
Perchlorate discharge test		
positive	11 (35%)	20 (65%)[b]
negative	20 (65%)	11 (35%)
Age at start L-T4 treatment (months)	0.7 (0.4; 0.9)	0.4 (0.3; 0.7)[a]
L-T4 dose at start (µg/k/d)	7.1 (5.6; 9.2)	9.1 (8.0; 10.4)[d]
L-T4 dose at 6 months of age (µg/k/d)	2.6 (2.1; 3.3)	3.9 (3.2; 4.9)[d]
L-T4 dose at 12 months of age (µg/k/d)	2.1 (1.7; 2.7)	3.2 (2.6; 3.8)[d]

P values below 0.05 are shown: a, $p<0.05$; b, $p<0.02$; c, $p<0.01$; d, $p<0.001$; Data are n (%) or median (25^{th}-75^{th} percentiles)

Familial CH: all but one of the affected relatives were siblings (the affected relative was the mother in the remaining case)

Table 2: Univariate and multiple logistic regression analysis: clinical predictors of transient CH

		Univariate analysis		Multivariate analysis	
	N of patients	Odds ratio (95% CI)	*p* values	Odds ratio (95% CI)	*p* values
Sex	92				
male		1	0.86		
female		0.93 (0.41-2.10)			
SGA	88				
no		1	**0.08**	1	0.81
yes		2.75 (0.89-8.55)		1.12 (0.23-6.36)	
Any neonatal problems (premature, SGA and/or neonatal distress)	92				
no		1	0.92		
yes		1.04 (0.45-2.39)			
Associated malformations or dysmorphic features	91				
no		1	**0.13**	1	0.84
yes		0.46 (0.17-1.25)		0.84 (0.16-4.33)	
Iodine overload	92				
no		1	**0.15**	1	0.46
yes		2.50 (0.72-8.65)		2.25 (0.26-19.81)	
Familial congenital hypothyroidism	90				
no		1	**0.02**	1	**0.03**
yes		0.09 (0.01-0.72)		0.04 (0.00-0.73)	
Serum TSH at diagnosis (mIU/l)	92	0.76 (0.64-0.90)	**0.001**	0.81 (0.61-1.07)	0.14
FT4 at diagnosis (pmol/l) (3 classes)	85		**0.07**		
≥ 10		1		1	0.72
5-9.9		0.47 (0.14-1.54)		0.58(0.10-3.53)	
<5		0.25 (0.07-0.90)		1.38 (0.10-19.16)	
Bone maturation at diagnosis (knee epiphyseal ossification centers)	86				
at least one present		1	0.53		
both absent		1.47 (0.44-4.93)			
Thyroid volume on ultrasound scan	88				
normal		1	**0.13**	1	0.20
hypoplastic/hemithyroid		0.22 (0.04-1.17)		0.18 (0.02-1.50)	
goiter		0.55 (0.21-1.44)		1.37 (0.2-9.4)	
L-T4 dose at 6 months of age (µg/k/d)	84	0.34 (0.19-0.59)	**0.0002**	0.49 (0.25-0.93)	**0.03**

Multivariate analysis revealed that **transient CH was associated with a lower likelihood of having a family history of CH (p = 0.03) and a lower levothyroxine dose at six months of age (p = 0.03) than permanent CH.**

Sex, neonatal problems, such as prematurity, being small for gestational age and/or neonatal distress, iodine status, coexisting malformations, initial CH severity and thyroid morphology at diagnosis had no effect. Ethnicity, consanguinity and the results of perchlorate discharge tests were not analyzed due to limited data availability.

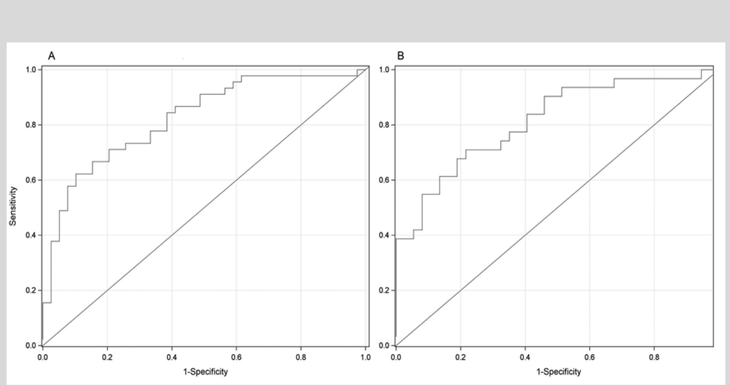

Figure 2
Receiver operating characteristics (ROC) curves for L-T4 dose at 6 (A) and 12 (B) months of age, for predicting transient congenital hypothyroidism.

·**At six months of age**, the area under the curve is 0.83, 95% CI (0.75-0.92). **For a cutoff value of 3.2 µg/kg/day, the sensitivity is 71% and specificity is 79%**.

·**At twelve months of age,** the area under the curve is 0.82, 95% CI (0.72-0.92). **For a cutoff value of 2.5 µg/kg/day, the sensitivity is 71% and specificity is 78%.**

Values below this threshold were considered predictive of transient CH.

SUMMARY

We identified two groups of children with CH and a eutopic gland:
·One group had the classical form of CH requiring long-term appropriate L-T4 therapy.
·The second group consisted of patients with transient CH, generally requiring lower doses of L-T4 and displaying the spontaneous resolution of CH within a few months.

CONCLUSION

·In patients with CH and a normally sited gland, these findings highlight **the need to evaluate levothyroxine dose requirement early, at six months of age,** particularly in patients with no family history of CH, for early identification of the **approximately 50% of patients for whom treatment should be stopped.**

·Parents should be made aware, when they are informed of their child's diagnosis during the neonatal period, that subsequent re-investigation will be necessary to determine whether the CH is persistent during childhood.

·However, the natural course of thyroid function of patients with transient CH during early childhood remains to be determined, and it is unknown whether these patients need to resume L-T4 treatment later in life during times of increased thyroxine need due to increases in metabolism, such as puberty and pregnancy.

57ESPE 248-P1
Thyroid
Carole Saba
Poster presented at: 57th ESPE 2018 Meeting ATHENS GREECE 27-29 September 2018
PosterSessionOnline.com