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 Zényati, L Martinerie, A Paulsen, D Simon, S Dos Santos, J Haiglène, D Mohamed, J 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.

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.

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 (25th-75th 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/kg/day.

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.

Figure 1 Flow chart of the study

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.

Table 1 Characteristics of patients with transient and permanent CH at 6 months of age

<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>Transient CH (n=67)</th>
<th>Permanent CH (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>19 (10-25)</td>
<td>19 (10-25)</td>
</tr>
<tr>
<td>Mass (kg)</td>
<td>5.93 (4.61-7.57)</td>
<td>5.91 (4.6-7.66)</td>
</tr>
<tr>
<td>Head circumference</td>
<td>38.32 (37.25-39.2)</td>
<td>38.4 (37.25-39.2)</td>
</tr>
<tr>
<td>Monthly gain in mass</td>
<td>650 (500-800)</td>
<td>600 (500-800)</td>
</tr>
<tr>
<td>Monthly gain in head circumference</td>
<td>2.5 (2-3)</td>
<td>2.5 (2-3)</td>
</tr>
</tbody>
</table>

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, coexistent 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.

- 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 78%.
- 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.