Guidelines for the management of congenital hypothyroidism in Scotland

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Summary

Diagnosis: screening test performed on newborn blood spot sample for elevated thyroid stimulating hormone (TSH).

Confirmatory tests (mandatory) pre-treatment thyroid function tests (TSH and free thyroxine – fT4) and quantitative thyroglobulin (TG).

Optional confirmatory tests may include thyroid imaging (ultrasound and/or radio-isotope scans of the neck, sub-lingual and upper chest area), thyroid autoantibodies (thyroid peroxidase and TSH receptor antibodies) in infant (and if indicated, mother) and maternal thyroid function tests (TFTs).

Treatment: replacement therapy with laevothyroxine.

Clinical aim:

1) To bring thyroid function into the normal range as rapidly as possible while avoiding adverse effects
2) To maintain fT4 in the upper half of the normal range and concurrent TSH in the normal range.
Screening laboratory notification protocol

**BIRTH**
(Cord blood for TFTs if previous sibling affected)

Newborn bloodspot test on Day 5 **irrespective** of infant’s health & feeding status (Ray 1997, Jones 2006) Now often occurs d4

Sample received by lab day 5-7, notified by lab day 6-12

- **TSH < 8 mU/L**
- **TSH 8 - 24 mU/L**
- **TSH ≥ 25 mU/L**

Lab request repeat

**NB** delay median 11 (1-52) days (Jones 2006)

- **TSH < 8 mU/L**
- **TSH ≥ 8 mU/L**

Reported as normal by laboratory to appropriate Community Child Health Record department

**REFERRAL**
Laboratory notification list

Referral procedure by laboratory: Laboratory staff notifying abnormal result **must speak directly** to a consultant paediatrician – either one of the two named paediatricians shown in the table below or the on-call paediatrician for the maternity unit. NB all results are notified simultaneously to Jez Jones at RHSC Glasgow.

Table 1 – Named paediatricians

<table>
<thead>
<tr>
<th>Centre</th>
<th>1st named paed</th>
<th>2nd named paed</th>
<th>Default</th>
</tr>
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<tbody>
<tr>
<td>Aberdeen</td>
<td>Mayo</td>
<td>Oxley</td>
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<tr>
<td>Ayrshire</td>
<td>Williamson</td>
<td>Staines</td>
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</tr>
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<td>Borders</td>
<td>Duncan</td>
<td>Ketteridge</td>
<td>”</td>
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<tr>
<td>Dumfries</td>
<td>Simpson</td>
<td>Chapman</td>
<td>”</td>
</tr>
<tr>
<td>Dundee</td>
<td>Conway</td>
<td>Fowlie</td>
<td>”</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>Bath</td>
<td>Midgely</td>
<td>”</td>
</tr>
<tr>
<td>Fife</td>
<td>Ainine</td>
<td>Menzies</td>
<td>”</td>
</tr>
<tr>
<td>Glasgow</td>
<td>Shaikh</td>
<td>Mason</td>
<td>”</td>
</tr>
<tr>
<td>Inverness</td>
<td>Farmer</td>
<td>Franklin</td>
<td>”</td>
</tr>
<tr>
<td>Lanarkshire</td>
<td>Hunter</td>
<td>Ibahnesebhor</td>
<td>”</td>
</tr>
<tr>
<td>Paisley</td>
<td>Conetta</td>
<td>Stewart</td>
<td>”</td>
</tr>
<tr>
<td>Stirling</td>
<td>Schulga</td>
<td>Colvin</td>
<td>”</td>
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Table 2 – Telephone numbers

<table>
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<tr>
<th>Centre</th>
<th>Switchboard</th>
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<tr>
<td>Aberdeen</td>
<td>0845 456 6000</td>
<td></td>
</tr>
<tr>
<td>Ayrshire</td>
<td>01563 521133</td>
<td></td>
</tr>
<tr>
<td>Borders</td>
<td>01896 826000</td>
<td></td>
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<tr>
<td>Dumfries</td>
<td>01387 246246</td>
<td></td>
</tr>
<tr>
<td>Dundee</td>
<td>01382 660111</td>
<td></td>
</tr>
<tr>
<td>Edinburgh</td>
<td>0131 536 0000</td>
<td></td>
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<tr>
<td>Fife</td>
<td>01592 643355</td>
<td></td>
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<tr>
<td>Glasgow</td>
<td>0141 201 0000</td>
<td></td>
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<tr>
<td>Inverness</td>
<td>01463 704000</td>
<td></td>
</tr>
<tr>
<td>Lanarkshire</td>
<td>01698 361100</td>
<td></td>
</tr>
<tr>
<td>Paisley</td>
<td>0141 887 9111</td>
<td></td>
</tr>
<tr>
<td>Stirling (Forth Valley)</td>
<td>01324 566000</td>
<td></td>
</tr>
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</table>
Procedure by clinician following notification

Clinician telephones GP and agrees method of contacting parents
(any of the following three are acceptable)

Clinician telephones family direct

GP telephones or visits family

Health visitor or midwife visits family

Baby must be seen on day of notification or next working day
(preferably on day of notification)

CLINICAL EVALUATION
Clinical evaluation

HISTORY – to include:

- Affected sibling
- Family history of thyroid illness/problems
- Thyroid disease or anti-thyroid therapy in mother
- Symptoms of hypothyroidism (eg poor feeding, sleepiness, jaundice, constipation, cold peripheries, hoarse cry).

EXAMINATION – to include:

- Weight, head circumference and length
- Measured (cf reported) parental heights (Cizmecioglu 2005)
- Presence or absence of goitre
- Signs of hypothyroidism (eg coarse facies, hoarse cry, umbilical hernia)

INITIAL INVESTIGATION:

- At least 1 ml of blood for TFTs in heparinised bottle or paediatric heparin tube filled to the line (be prepared to make several attempts in order to get sufficient blood)
- 1 ml clotted blood for quantitative thyroglobulin (Mitchell 1995, Djemli 2004)
This decision tree is based on the following evidence taken from the Scottish CH database. This evidence compares screening TSH values with pre-treatment thyroid function test results in otherwise well, term infants. As expected, if an infant has a screening TSH of >100 mU/l then there is an 84% chance that they will have a sub-normal fT4 (<9.0 pmol/l) and a 4.5% chance that they will have a fT4 in the upper half of the normal range. What is surprising is that even with a screening TSH of between 8.0 and 20 mU/l there is a >10% chance that any given infant will have a sub-normal fT4. Do NOT delay treatment unless there are no features or signs of hypothyroidism in the infant on careful examination and history.
<table>
<thead>
<tr>
<th>Screening TSH (mU/L)</th>
<th>Total patients</th>
<th>Number (%) with fT4 &lt;9 pmol/L</th>
<th>Number (%) with fT4 9-15 pmol/L</th>
<th>Number (%) with fT4 &gt;15 pmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;100</td>
<td>310</td>
<td>260 (83.9)</td>
<td>36 (11.6)</td>
<td>14 (4.5)</td>
</tr>
<tr>
<td>75 - 100</td>
<td>23</td>
<td>8 (34.8)</td>
<td>6 (26.1)</td>
<td>9 (39.1)</td>
</tr>
<tr>
<td>50 - 74</td>
<td>45</td>
<td>8 (17.7)</td>
<td>11 (24.4)</td>
<td>26 (57.8)</td>
</tr>
<tr>
<td>40 - 49</td>
<td>27</td>
<td>5 (18.5)</td>
<td>6 (22.2)</td>
<td>16 (59.3)</td>
</tr>
<tr>
<td>30 - 39</td>
<td>16</td>
<td>2 (12.5)</td>
<td>6 (37.5)</td>
<td>8 (50.0)</td>
</tr>
<tr>
<td>20 - 29</td>
<td>30</td>
<td>4 (13.3)</td>
<td>9 (30.0)</td>
<td>17 (56.7)</td>
</tr>
<tr>
<td>8 - 20</td>
<td>26</td>
<td>3 (11.5)</td>
<td>9 (34.6)</td>
<td>14 (53.8)</td>
</tr>
</tbody>
</table>

**Dosage schedule**

Dosage schedule for infant with elevated TSH, if treatment is recommended (see decision tree)

- **Initial LT4 50 µg/day** *(Jones 2008)*  
  **NB** if birth weight <2.5 kg then 15 µg/kg

- **Maintain dose until TSH <5 mU/L** *(Bongers-Schokking 2000, Selva 2005, Jones 2008)*

- **Then LT4 37.5 µg/day** *(Jones 2008)*

- Thereafter titrate dose to keep fT4 >15 pmol/L and TSH < 5.0 mU/L

**NB** Assume venous TFT result will be available >1 day after referral.
Preparations of thyroxine

Replacement laevothyroxine is available in two forms – either tablets or commercial liquid (Evotrox).

Written instructions should be available and supplied to the parents.

Tablets

Available as 25 µg or 50 µg. Tablets should be crushed and mixed with a small volume (< 5ml) of liquid (formula, expressed breast milk or boiled and cooled water). Supply a tablet cutter for halving tablets.

The first dose should be given by parents under the supervision of a nurse or pharmacist.

Evotrox liquid thyroxine NB - NOW WITHDRAWN

Therefore there are NO recommended liquid forms of thyroxine available including syrups, solutions and suspensions

This is supplied in 100 ml bottles and is available in 3 strengths:

25 µg/5ml = 5 µg/ml (therefore a 50 µg daily dose = 10 ml and a 37.5 µg daily dose = 7.5 ml)

50 µg/5ml = 10 µg/ml (therefore a 50 µg daily dose = 5 ml and a 37.5 µg daily dose = 3.75 ml)

100 µg/5ml = 20 µg/ml (therefore a 50 µg daily dose = 2.5 ml and a 37.5 µg daily dose = 1.875 ml)

NB There is no available published comparison of Evotrox with tablet thyroxine.
Initial counselling and management

Essential information at initial visit

- Thyroid hormone vital for normal brain development and somatic growth;
- Thyroid gland either absent, too small or not producing thyroid hormone properly;
- Probably permanent;
- Good prognosis;
- Compliance crucial, especially from birth to 3 years of age when brain developing most rapidly;
- Easy treatment to administer;
- Verbal and written instructions on how to give medicines.

Give the thyroid booklet from the Child Growth Foundation and BSPED (or SPEG information on CH?).

Thyroid imaging

Where and when available: offer all families opportunity for their babies to undergo thyroid imaging because:

- More informative than blood tests alone;
- Will aid in genetic counselling;
- Likelihood of lifelong treatment if proven permanent CH;
- Provides a useful guide as to thyroxine dose (Mathai 2008).

Combined isotope and ultrasound imaging (dual scanning) available in Glasgow. Isotope imaging available in Aberdeen, possibly in conjunction with ultrasound imaging.

Isotope scans should be performed by day 5 of start of treatment (Perry 2006) to ensure avoidance of false negatives, due to TSH suppression (advisable to take thyroid function sample on day of scans to confirm reliability of results).

Mutation analysis in suspected cases of dyshormonogenesis

If thyroid imaging suggests that the cause of the hypothyroidism might be due to an enzyme defect in the function of the thyroid, there is now a mutation analysis service available in Scotland. This is based in the laboratories at the Southern General Hospital. The service offers analyses for the three most common mutations responsible for dyshormonogenesis in Scotland, namely mutations in thyroperoxidase (TPO), thyroglobulin (Tg) and the TSH receptor (TSHR).

Sample type is EDTA blood and the lab requires at least 1 ml.

The service is managed by Dr Therese Bradley who can be contacted on:

Therese.Bradley@ggc.scot.nhs.uk
Or by telephone on 0141 354 9330
**Subsequent monitoring and follow-up.**

Initial visit in Scotland occurs on day 11 of life *(Jones 2006)*

First subsequent visit should be on or before day 7 of treatment (ie day 18 of life)

**At this visit:**
- Carry out thyroid imaging if applicable
- Ensure that fT4 is in the normal range
- Ensure that the family is OK
- Provide further counselling

Next visit should be one week later (by day 25)

Further visit should be one week later (by day 32)

**Suggested follow-up intervals after one month of age**

<table>
<thead>
<tr>
<th>From (age)</th>
<th>Until (age)</th>
<th>Suggested interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td>6 months</td>
<td>2 – 4 weeks</td>
</tr>
<tr>
<td>6 months</td>
<td>1 year</td>
<td>4 – 8 weeks</td>
</tr>
<tr>
<td>1 year</td>
<td>3 years</td>
<td>4- 6 months</td>
</tr>
<tr>
<td>3 years</td>
<td>Completion of growth</td>
<td>Annual (if reasonable compliance)</td>
</tr>
</tbody>
</table>

**NB** We would also suggest additional clinic visits following dosage alteration or when there are problems with poor compliance
What to do at each visit

1. Calculate optimal dose and adjust dosage **pre-emptively** (see table at foot of page), using TFTs to confirm compliance.

2. Growth
   - weight
   - length until 2 years, then height
   - head circumference until 3 years

3. Development
   - consider pre-school formal audiology (for subtle hearing impairment due to CH)
     - if aged <4-5 years, developmental progress
     - aged ≥ 4-5 years, school progress

4. Education
   - from secondary school onwards ensure that patient has reasonable knowledge of CH.

5. Adult transfer at 14-15 years.
   - Boys – to GP (unless problems with control
   - Girls – to adult endocrinology (for pre-pregnancy counselling).

Thyroxine dosage at each visit

**Aim:** fT4 > 15 pmol/l and TSH <5.0 mU/l

<table>
<thead>
<tr>
<th>Newborn period to 3 years</th>
<th>full replacement dose (ie for athyreotic patient) is likely to be:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td><strong>LT4 dose (µg daily)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Female</strong></td>
</tr>
<tr>
<td>3 months</td>
<td>41.3</td>
</tr>
<tr>
<td>6 months</td>
<td>45.8</td>
</tr>
<tr>
<td>9 months</td>
<td>47.9</td>
</tr>
<tr>
<td>12 months</td>
<td>55.0</td>
</tr>
<tr>
<td>18 months</td>
<td>62.5</td>
</tr>
<tr>
<td>24 months</td>
<td>70.3</td>
</tr>
<tr>
<td>36 months</td>
<td>75.0</td>
</tr>
</tbody>
</table>
References


5. Jones JH, Neumann D and Donaldson MDC. Predictive value of newborn blood spot (Guthrie) thyroid stimulating hormone level in severity of congenital hypothyroidism. (In preparation).


