Screening for Congenital Hypothyroidism: Comparison of Borderline Screening Cut-Off Points and the Effect on the Number of Children Treated with Levothyroxine

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Key Words
Newborn screening · Levothyroxine · Congenital hypothyroidism · Thyroid-stimulating hormone

Abstract
Background: The newborn screening programme for congenital hypothyroidism (CH) has led to the prevention of severe developmental delay associated with this condition. In the UK, thyroid-stimulating hormone (TSH) screening cut-off points have changed over time, in some instances prompted by changing methodological platforms. The use of borderline cut-off points varies throughout the country.

Objective: To use discordance in cut-off points to assess the performance of the UK Newborn Screening Programme Centre (UKNSPC) definitions.

Methods: Between January 2006 and December 2007, 223,658 newborn infants were screened by the Great Ormond Street Hospital (GOSH) for CH. All children with positive results and those with blood-spot TSH concentrations >6 mU/l on repeat screening were referred to GOSH. We compared the numbers of children detected and treated for CH using the GOSH cut-off points (>6 mU/l) and those of the national screening programme (>10 mU/l). Children were defined as transient CH if levothyroxine treatment had been discontinued by 3 years.

Results: Of the children screened between January 2006 and December 2007, 167 out of 223,658 fulfilled the GOSH screening criteria; 136 of these required levothyroxine treatment, but 29 (21%) of the children treated would not have been detected by the current UKNSPC guidelines. Transient CH was found in 17/47 (36%) of the treated children detected with a cut-off point >6 mU/l. Raising the cut-off point to >10 mU/l reduced the number of children treated for transient CH to 4/18 (22%).

Conclusion: A significant number of children with true and transient CH are missed with a screening cut-off point of >10 mU/l. Our data suggests that a cut-off point of 6 mU/l is appropriate.

Introduction
The newborn screening programme for CH was introduced in the UK in 1981 [1, 2] and has virtually abolished cases of untreated congenital hypothyroidism (CH). CH is a common (1 in 3,000–4,000 live births) condition [3, 4] in which the thyroid gland has either failed to develop (agenesis or dysgenesis) or there is a defect in thyroid hormonogenesis (dyshormonogenesis). In the neonatal stage and early childhood years, levothyroxine is essential for normal brain development [5, 6], so early diagnosis and instigation of therapy are essential to allow normal neurodevelopment.

The UK Newborn Screening Programme Centre (UKNSPC) has defined standards for the screening process [2, 7], using thyroid-stimulating hormone (TSH) as
a biomarker. Screening results for CH are considered positive when the bloodspot TSH concentration exceeds 20 mU/l and borderline when the concentration ranges between 10 and 20 mU/l [2]. A repeat bloodspot is taken 1 week later in cases of borderline bloodspot concentrations. All positive and double-borderline cases are referred for paediatric review.

The practice at the Great Ormond Street Hospital (GOSH) Newborn Screening laboratory which covers the North Thames region and has a high screening throughput (117,000 infants screened per annum) has differed from this in that the lower borderline concentration used is 6 rather than 10 mU/l. This discordance in cut-off points arose in part from a recalibration of the TSH assay when moving from the immunoradiometric assay (Immunodiagnostic Systems, Boldon, Tyne and Wear, UK) and the observation that several individuals with a screening TSH concentration between 6 and 12 mU/l went on to require levothyroxine therapy [8], an observation subsequently noted by others [9]. We have used this discordance in lower cut-off points to assess the performance of the UKNSPC definitions using a defined protocol of assessment.

**Methods**

Between January 2006 and December 2007, a total of 223,658 newborn infants were screened by the GOSH for CH. With the exception of infants tested in neonatal units, all the positive cases and borderline cases diagnosed in the newborn screening programme with a repeat bloodspot TSH >6 mU/l were referred to the Endocrine Team at the GOSH.

At review, referred babies underwent confirmatory testing with a measurement of serum TSH, free thyroxine (FT4) concentrations and thyroid autoantibodies. Maternal thyroid function and autoantibody status were also checked in babies confirmed to have CH. All infants with a serum TSH concentration >15 mU/l underwent a radio isotopic technetium scan to determine the position and functionality of the thyroid gland. Details of gestational age (prematurity defined as <37 weeks) and ethnicity were recorded from the newborn screening card and checked on presentation to the Endocrine Team. For children tested in neonatal units, the Endocrine Team contacted the unit and advised on further management and blood monitoring.

Treatment with levothyroxine (8–12 μg/kg body weight) was commenced if the serum FT4 was below the normal range for gestational age. In individuals with elevated serum TSH concentration and normal serum FT4 concentration, further follow-up was undertaken 1–2 weeks later. Levothyroxine was commenced if there was a further elevation of the TSH or a fall in FT4. Long-term follow-up was provided at GOSH or with a local, designated paediatrician. At GOSH, it is our practice to stop levothyroxine in children at the age of 3 years if they remain on small doses of thyroxine (<25 μg) and trial off therapy. For patients managed locally, we were able to access details of whether or not they remained on levothyroxine therapy at 3 years of age. Those who had discontinued treatment were considered to have had a diagnosis of transient CH.

Bloodspot TSH concentrations were measured by the automated dissociation-enhanced lanthanide fluorimunoassay (AutoDELFIA, Perkin Elmer, UK) system whereas serum TSH and FT4 concentrations were measured by chemiluminescent immunometric assay (Immulete 2000, Diagnostic Products, Gwynedd, UK). TSH results were expressed as a mean of triplicate results from three separately punched blood spots. Results were given to one decimal place.

**Analysis**

To allow comparison with the UKNSPC guidelines, TSH values >20 mU/l are presented as positive and 10–19.9 mU/l as borderline on the first screen. These cut-off points were then compared to the additional information generated by operating the GOSH lower borderline cutoff point of 6 mU/l. All data are presented as percentages. Differences between groups with different TSH cut-off points were tested with χ² tests.

**Results**

**General**

Using the GOSH lower borderline cut-off point, there were 222,907 out of the total of 223,658 babies screened with a TSH value <6 mU/l and no further action was required (fig. 1). There were 93 babies referred to the Endocrine Team with a TSH concentration >20 mU/l (considered positive) 89 of whom received treatment; 3 had normal venous FT4 with normalisation of the TSH and

![Fig. 1. Neonates referred to endocrine service after initial TSH blood spot results.](image-url)
1 child is under investigation for a possible TSH receptor mutation.

For the remaining children with values of 6–19.9 mU/l on initial TSH screening, by applying the UKNSPC cut-off point of 10 mU/l, there were 170 babies who required a repeat test, whereas the GOSH cut-off value of 6 mU/l led to the re-testing of an additional 488 babies (fig. 1). Therefore, of the 223,658 newborn infants screened, a total of 167 children were referred to the GOSH Endocrine Team after meeting the referral criteria (fig. 1).

**Borderline Screening Results**

Seventy-four babies with an initial borderline screening TSH of 6–19.9 were referred to the Endocrine Team for assessment after repeat TSH bloodspot screening. Of these, 12 were found to have a repeat TSH blood spot ≥20 and the other 62 were identified as double-borderline, with two screening TSH results ranging from 6 to 19.9 mU/l.

**Initial Blood Spot TSH 10–19.9 mU/l**

There were 170 babies with an initial TSH value of 10–19.9 mU/l, 140 (82.4%) had a repeat TSH <6 mU/l and no further action was undertaken. The repeat screening on the remaining babies detected 7 (4.1%) with a TSH >20 mU/l, 16 (9.4%) with a TSH 10–19.9 mU/l and 7 (4.1%) with a TSH 6–9.9 mU/l (fig. 2). After serum thyroid function tests were performed, there were 6/7 children with a TSH >20 mU/l and 12/16 with a TSH 10–19.9 mU/l who required treatment with levothyroxine. However, an additional 4/7 babies with a repeat TSH 6–9.9 mU/l who would not have been called for review under UKNSPC guidelines were also treated with levothyroxine.

**Initial Blood Spot TSH 6–9.9 mU/l**

Four hundred and eighty-eight babies were found to have an initial TSH value of 6–9.9 mU/l. On repeat screening, this was <6 mU/l in 444 (91%) of them, and no further action was undertaken. There were 5 (1.0%) children with a TSH >20 mU/l, 9 (1.8%) with a TSH 10–19.9 mU/l and 30 (6.1%) with a TSH 6–9.9 mU/l (fig. 3). After review and thyroid function tests, the numbers that subsequently required treatment with levothyroxine were 4/5 children with a TSH >20 mU/l, 7/9 with a TSH 10–19.9 mU/l and 14/30 with a TSH 6–9.9 mU/l. If based on the UKNSPC guidelines, none of these children would have been investigated or treated.

**Comparison of Outcomes Based on Cut-Off Points**

In the group of newborns who were referred with an initial borderline TSH result (6–19.9 mU/l), there was a total of 47 who required treatment with levothyroxine. According to the UKNSPC guidelines, 29 (62%) of these would not have been detected. This group includes all 25 treated children with an initial TSH 6–9.9 mU/l (fig. 3) plus 4 treated children who had an initial TSH of 10–19.9 mU/l, but a repeat TSH of 6–9.9 mU/l (fig. 2).
Distribution of Ethnicity with Respect to Screening Cut-Off Points

For the 136 infants started on levothyroxine treatment, the distribution of recorded ethnicity was examined with respect to the TSH cut-off points (table 1). White and Asian (Indian subcontinent) groups were the most represented and the distribution between cut-off points was similar. The ethnic distribution included 64 (47%) White, 43 (32%) Asian and 8 (6%) Black. This suggests an over-representation of newborns requiring treatment from Asian backgrounds compared to the population screened. There were no differences in ethnic distribution between treated babies with borderline cut-off points of 6–9.9 mU/l or 10–19.9 mU/l.

Table 1. Relationship between ethnicity, gestation and technetium scan results to initial TSH cut-off points for babies treated with levothyroxine

<table>
<thead>
<tr>
<th>TSH cut-off points (mU/l)</th>
<th>Ethnicty (p = 0.61)</th>
<th>Gestation (p = 0.59)</th>
<th>Technetium scan (p &lt; 0.001)*</th>
<th>TPO antibodies (p = 0.11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–9.9</td>
<td>White: 11 (44)</td>
<td>Term: 18 (72)</td>
<td>Agenesis/Dysgenesis: 0</td>
<td>Positive: 2</td>
</tr>
<tr>
<td></td>
<td>Mixed Race: 2 (8)</td>
<td></td>
<td>Ectopic: 0</td>
<td>Negative: 13</td>
</tr>
<tr>
<td></td>
<td>Asian: 7 (28)</td>
<td></td>
<td>Dyshormonogenesis: 9 (36)</td>
<td>Not performed: 13</td>
</tr>
<tr>
<td></td>
<td>Black: 4 (16)</td>
<td></td>
<td>Two Foci: 1 (4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other: 1 (4)</td>
<td></td>
<td>Mild Dysplasia: 2 (8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not recorded: 1</td>
<td></td>
<td>Normal: 0</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10–19.9</td>
<td>White: 8 (36)</td>
<td>Term: 18 (82)</td>
<td>Agenesis/Dysgenesis: 3 (14)</td>
<td>Positive: 1</td>
</tr>
<tr>
<td></td>
<td>Mixed Race: 2 (9)</td>
<td></td>
<td>Ectopic: 1 (4.5)</td>
<td>Negative: 17</td>
</tr>
<tr>
<td></td>
<td>Asian: 9 (41)</td>
<td></td>
<td>Dyshormonogenesis: 11 (50)</td>
<td>Not performed: 4</td>
</tr>
<tr>
<td></td>
<td>Black: 1 (5)</td>
<td></td>
<td>Two Foci: 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other: 2 (9)</td>
<td></td>
<td>Mild Dysplasia: 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not recorded: 3</td>
<td></td>
<td>Normal: 1 (4.5)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&gt;20</td>
<td>White: 45 (51)</td>
<td>Term: 71 (80)</td>
<td>Agenesis/Dysgenesis: 21 (24)</td>
<td>Positive: 4</td>
</tr>
<tr>
<td></td>
<td>Mixed Race: 6 (2)</td>
<td></td>
<td>Ectopic: 3 (14)</td>
<td>Negative: 21</td>
</tr>
<tr>
<td></td>
<td>Asian: 27 (30)</td>
<td></td>
<td>Dyshormonogenesis: 15 (17)</td>
<td>Not performed: 27</td>
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<tr>
<td></td>
<td>Black: 3 (3)</td>
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<td>Two Foci: 2 (10)</td>
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<td>Other: 5 (6)</td>
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<td>Mild Dysplasia: 0</td>
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<tr>
<td></td>
<td>Not recorded: 3</td>
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<td>Normal: 1 (4.5)</td>
<td></td>
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<tr>
<td>Total (136)</td>
<td>25</td>
<td>22</td>
<td>89</td>
<td>Total (136)</td>
</tr>
</tbody>
</table>

Figures in parentheses are percentages. TPO = Thyroperoxidase. * Technetium scan uptake showed no influence of either ethnicity (p = 0.38) or prematurity (p = 0.53).

Gestation

The ratio of term:preterm babies who were treated in the positive group and the group with 10–19.9 mU/l was the same, but was slightly less in the group with 6–9.9 mU/l, suggesting a possible slight over-representation of premature babies in this group, but the overall numbers of treated preterm babies in the borderline groups were small (table 1).

When analysing only the borderline group with a first blood spot TSH of 6–19.9 mU/l, there is further evidence of an over-representation of premature infants with a total of 74 babies (26 preterm and 48 term). However, a higher percentage of term babies (75% or 36/48) than preterm babies (42% or 11/26), were started on levothyroxine. Only 15/36 term and 3/11 preterm babies would have been treated if borderline referrals had been dependent on two blood spot results being >10 mU/l (fig. 4).

Relationship with Results of Technetium Scan

The results of thyroid scans in the infants receiving treatment with levothyroxine are shown in table 1. Technetium scans were not performed in 52% of newborns with an initial TSH of 6–9.9 mU/l or in 27% of those with an initial TSH of 10–19.9 mU/l. The majority of scan results in these 2 borderline groups was consistent with dyshormonogenesis, compared with the high proportion of agenesis and ectopia in those with a positive screening TSH concentration of >20 mU/l.

Thyroid Autoantibodies

Thyroid peroxidase antibodies were positive in 7 treated newborns (mothers: 6 positive and 1 was not done). Of these, the initial TSH results were TSH >20 mU/l in 4 patients (2 agenesis and 2 normal scan), TSH 10–19.9 mU/l in 1 patient (dyshormonogenesis) and TSH 6–9.9 mU/l in 2 patients (no scan). Four of the 7 children remained on levothyroxine at 3 years of age (2 agenesis, 1 dyshormonogenesis and 1 not done). A further 4 treated babies were antibody-negative despite detection of antibodies in the mother (2 had TSH >20 mU/l and 2 had TSH 10–19.9 mU/l).

Outcome at Three Years for Children Started on Thyroxine

Of the 47 newborns started on thyroxine after initial borderline TSH screening results, 29 (62%) remained on this treatment at the age of 3 years (fig. 2, 3). One child was lost to follow-up. If this group had been limited to those with a double-borderline cut-off of ≥10 mU/l,
18 babies would have started on thyroxine, 14 (78%) of whom would have remained on treatment at 3 years (fig. 2).

This suggests that the percentage of transient CH detected with a screening cut-off of 6 mU/l is 45% (13/29) compared with 55% with confirmed CH. This is compared to 22% transient CH cases and 78% confirmed CH cases in those with double-borderline results of >10 mU/l.

**Conclusion**

The introduction of newborn screening for CH has been a major public health success. It has greatly improved the neurodevelopment outcome of children who may otherwise only have been diagnosed later in life. Prior to the introduction of the screening programme, it had been estimated that in the UK, 29% of children with CH required specialist schooling [10]. The cost-benefit analysis of the CH screening programme has been based on the economic benefits of the prevention of severe developmental delay. Growth delay and behavioural abnormalities are also recognised associations of CH.

TSH cut-off points have been lowered over time to improve detection rates and as a consequence of changes made to the assay methods. Positive cut-off points are chosen to ensure that the most severe forms of CH are detected; in our study, the UKNSPC guidelines picked up all cases of agenesis and ectopic CH. Difficulties in interpretation arise with the use of borderline cut-off points. Concern that a rising TSH may be missed has led to the introduction of borderline cut-off points that indicate the need for a repeat blood spot after a delay of 1 week.

Bloodspot TSH concentrations will fall across a continuous spectrum into the normal range and screening provides a result for a single point in time in a dynamic thyroid axis that includes a physiological postnatal TSH surge. A delay in this postnatal surge, the presence of antibodies and iodine status may all influence the initial screening results leading to positive or borderline results. The slightly higher relative numbers of preterm babies seen in our study may represent the immaturity of this axis.

The use of a borderline cut-off point will increase the detection of CH [11, 12] and will inevitably pick up less severe cases. There is no evidence of where the lower cut-off point should sit and the UKNSPC value of 10 mU/l has been set by expert personal opinion with no subsequent evidence to support or refute this standard. There is variation in practice across the UK, with different centres using cut-off points between 5–10 mU/l.
We have attempted to provide some evaluation of these cut-off points in our own cohort and have used treatment outcomes to compare UKNSPC with GOSH. Children treated with levothyroxine in this study either had an FT4 below the normal reference range or evidence of a continuing rise in TSH or fall in FT4 and were considered to have CH rather than persistent hyperthyrotoxia.

From our data, 136 of the 223,658 children screened required levothyroxine treatment. Of these, 29 treated children would not have been picked up by the current UKNSPC guidelines; 15 of these remained on levothyroxine at 3 years. This indicates that a significant number of children with permanent and transient CH are missed with a borderline screening cut-off point of >10 mU/l.

Our transient CH data are consistent with published data [13]. This phenomenon was seen in all screening groups, but was increased with the lower cut-off points. It is not currently possible to predict those that will have transient or permanent CH based on initial biochemistry results, and thus, at present, there is a need to treat all. The underlying diagnosis in the group of children with transient CH is often not elucidated and may include cases resulting from maternal antibody transmission, immaturity of the thyroid axis or iodine deficiency or excess. Details of iodine status in this cohort were not collected. It is difficult to assess the possible benefits of this early treatment of the transient CH cases. These children may remain at longer-term risk of subclinical hypothyroidism [14] and it is unknown whether children with transient hypothyroidism may require recommencement of levothyroxine treatment in later life at times of increased growth and metabolism, such as puberty and pregnancy.

The more difficult question to address is the precise value of borderline cut-off points per se. There would be few paediatricians who would not treat babies with a persistently raised TSH or FT4 below the normal range, and it is thus difficult to ethically study the neurodevelopmental impact of the diagnosis and treatment of neonates detected with variable screening concentrations of TSH after the introduction of the screening programme. Although UK screening centres use different lower cut-off points, decision to treat is dependent on subsequent serum TFT and retrospective analysis across the UK of the screening group with 6–9.9 mU/l would therefore not be possible.

The continuous spectrum of TSH concentrations may reflect a continuous spectrum of intellectual and clinical effects from severe to negligible, although extrapolating the outcomes of studies of those with severe CH for those with only mild or transient CH [15] is likely to be misleading. Retrospective screening studies do suggest that subclinical CH may lead to an average decrease of seven IQ points [15, 16]. Whilst this may not equate to severe intellectual disability, it represents a significant reduction in IQ potential, particularly for individuals in the lower IQ range. In addition, these children are also at risk of behavioural problems and possible impaired growth. There is also evidence that children with CH who are treated early remain at risk of intellectual difficulties [17]. Differences in school achievement, particularly verbal and arithmetic skills may be related to suboptimal levothyroxine replacement [18]. This raises the possibility that children with untreated mild or transient hypothyroidism may be exposed to similar risks.

Our study demonstrates that the current UKNSPC guidelines miss cases of permanent and transient CH in the borderline screening groups, compared to the lower GOSH cut-off points. We examined data from one screening centre, ensuring a consistent approach to the diagnosis and decision to treat. There is little difference between the infants detected and treated from the group with 6–9.9 mU/l to the group with 10–19.9 mU/l. Therefore, where a double-borderline group exists as part of the screening programme, we would recommend lowering the cut-off point to include these children.

Disclosure Statement

No interests to declare.

References


