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Evaluation of the revised New Zealand national newborn screening protocol for congenital hypothyroidism

Short Title: Newborn screening for congenital hypothyroidism in New Zealand

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ABSTRACT

Objective: To assess the performance of the revised New Zealand (NZ) newborn screening TSH cut-offs for congenital hypothyroidism (CHT).

Methods: Screening data over 24 months were obtained from the NZ newborn metabolic screening programme, which utilizes a 2-tier system of direct clinical referral for infants with markedly elevated TSH, and second samples from those with mild TSH elevation. We evaluated the impact of a reduced TSH threshold (50 to 30 mIU/L blood) for direct notification and a lower cut-off (15 to 8 mIU/L blood) applied to second samples and babies older than 14 days.

Results: In 2013 and 2014, 117,528 infants underwent newborn screening for CHT. 52 CHT cases were identified by screening (47 general newborn population, 5 repeat testing in low-birth-weight infants) and one case was missed. 32 infants with screening TSH ≥30 mIU/L were directly referred at a median of 9 days (5-14) and 15 with TSH 15-29 mIU/L were referred after a second card at a median of 20 days (9-52, $p<0.001$). All directly referred infants were confirmed as CHT cases with no earlier referrals as a result of the reduced threshold. The lower TSH cut-off applied to second samples lead to the identification of 6 extra cases of CHT (15% increase) from 7 extra clinical referrals.

Conclusions: The NZ screening programme achieved a 15% increase in CHT case detection for minimal increase in workload or anxiety for families of healthy infants. A further decrease in the threshold for direct referral may allow earlier diagnoses.

INTRODUCTION

Congenital hypothyroidism (CHT) is a common preventable cause of intellectual disability [1, 2]. Early treatment for CHT detected by newborn screening is highly successful, such that even those with severe disease can be anticipated to have normal intellectual outcomes [3]. Furthermore, CHT is one of few conditions where screening costs are calculated to be less than the treatment of disability [4]. Screening strategies are based either on detection of low thyroxine or elevated thyroid-stimulating hormone (TSH), with the latter a more sensitive means of detecting mild primary hypothyroidism [2]. Given the success of screening for CHT and the inevitable drive to diagnose and treat increasingly milder disease, TSH cut-offs have decreased markedly from inception. The current screening dilemma is to define optimal TSH thresholds that appropriately balance the benefits of disease detection with harms from false-positive results in healthy infants [1, 5].

Several programs have reported their experience with decreased TSH cut-offs. When two European programs decreased TSH cut-offs from 20 to 10 mIU/L blood, the incidence of CHT detected increased from 3.4 to 4.8 per 10,000 [6] and 3.8 to 8.7 per 10,000 [7] (the latter possibly due to co-incident mild regional iodine deficiency). Both groups reported that the proportion of cases with a normally positioned (*in situ*) thyroid gland and presumed functional deficits increased [6, 7]. Langham et al. reported that, where the TSH cut-off used by the Great Ormond Street Hospital Newborn Screening laboratory in the United Kingdom was decreased from 10 to 6 mIU/L blood, the proportion of transient cases doubled (from 22% to 45%, total CHT incidence increased from 4.8 to 6.1 per 10,000) [8].

Whilst we can be confident that infants with severe CHT will benefit from early identification, the evidence that screening benefits infants with mild, subclinical, and transient disease is less clear [1, 5]. In a landmark retrospective study from Sweden, TSH screening was performed on stored blood collection cards and elevated TSH (>20 mIU/L blood) identified in 32 individuals [9]. Poor intellectual outcomes were seen in those who had been diagnosed as clinically hypothyroid (likely the most severe cases, diagnosed at a median age of 5 months). In contrast, outcomes were surprisingly good for those who had not received a clinical diagnosis despite persistently elevated TSH at 5 years (mean developmental quotient 100). As TSH screening cut-offs decrease, further cases of mild CHT will be detected, with the assumption that these children are at risk of subtle cognitive impairment. However, the natural history of mildly elevated neonatal TSH is poorly understood, and the benefits of extending CHT screening to include these cases are unclear [1, 5].

The New Zealand newborn metabolic screening programme (NMSP) has used the same TSH assay and consistent cut-offs between 1997 and 2012 (Fig. 1). It is a 2-tier system whereby infants with markedly elevated TSH are directly referred to a paediatric endocrinologist, and second samples are requested from those with mild TSH elevation (Fig. 1). Screening cut-offs were reviewed in 2012, in

a process that involved international comparisons, statistical modeling, and review of missed cases. Following this, the whole blood TSH threshold for direct clinical notification was decreased from 50 to 30 mIU/L (Fig. 2). The lower TSH cut-off remained ≥15 mIU/L, but a reduced threshold of ≥8 mIU/L was applied to older babies and repeat samples (Fig. 2).

The aim of this study was to assess the performance of the revised New Zealand screening algorithm over 24 months. In particular, we aimed to determine the number of extra CHT cases identified for the number of increased clinical referrals.

METHODS

New Zealand has an annual birth rate of approximately 60,000, and newborn metabolic screening has an estimated coverage of >99% live births. Heel-prick samples are collected on paper 48-72 hours after birth, usually obtained in the community by the lead maternity carer. Samples are subsequently posted to the laboratory located in Auckland, which is the single facility conducting all newborn screening TSH tests in the country.

New Zealand introduced newborn screening for CHT in 1981, and adopted a TSH-only screen in 1986. The Perkin-Elmer Delfia assay has been used to measure whole blood TSH since 1997. Unless otherwise specified, all TSH levels in the manuscript refer to whole blood screening samples. From 1997 to 2012, infants with TSH ≥50 mIU/L were directly referred to a paediatric endocrinologist. Lead maternity carers were asked to collect a second samples from infants who had TSH 15-50 mIU/L on their initial screen, with infants subsequently referred to a paediatric endocrinologist if TSH remained ≥15 mIU/L. A separate protocol for routine repeat sampling of low-birth-weight infants was introduced in 2007, whereby a

second routine heel-prick sample is taken from infants with birthweight <1500 g at 2 weeks of age, and a third at 4 weeks of age from infants <1000 g.

The cut-offs used in the screening algorithm were revised in January 2013 (Fig. 1). The revised threshold for direct paediatric endocrine referral was reduced to TSH ≥30 mIU/L. Although the overall TSH threshold for request of a repeat sample was not changed (15-30 mIU/L), the threshold for request of a second sample was decreased in older babies (>14 days of age, repeat sample requested if TSH ≥8 mIU/L) and all infants were referred to a paediatric endocrinologist for definitive evaluation if the second sample TSH was ≥8 mIU/L.

Data collection and analyses

Newborn screening data for possible cases of CHT were obtained from NMSP records. In addition, the NMSP collects clinical data on infants referred by means of standardised forms sent out to paediatric endocrinologists. CHT was defined as a positive screen, followed by confirmatory serum TSH ≥15 mIU/L. Aetiology was classified based on thyroid scintiscan or ultrasound as dysgenesis (athyreosis or an ectopic gland) or dyshormonogenesis (a normally-sited gland with normal or increased size and technecium uptake).

Cases that were directly notified were compared to those notified after a second sample. Demographic data were compared using one-way analysis of variance and chi-square tests. Clinical data were analysed using non-parametric Kruskal-Wallis tests, chi-square test, and Fisher's exact test. Statistical tests were two-tailed and significance level maintained at 5%.

RESULTS

In 2013 and 2014, 117,528 infants underwent newborn screening for CHT in New Zealand. There were 52 CHT cases identified by screening (47 from the general screening algorithm and 5 from repeat testing of low-birth-weight infants), and we are aware of 1 case that was missed by screening (Fig. 3). Thus, the population incidence of CHT was 1:2218, and the positive predictive value (PPV) of CHT given an elevated screen result (initial TSH ≥15 mIU/L, 47/76) was 61.8%.

Direct Referrals

32 infants with markedly elevated TSH (≥30 mIU/L) were directly referred to a paediatric endocrinologist, and were all subsequently diagnosed with CHT (PPV 100%). The median TSH for this group was 143 mIU/L (range 62-354 mIU/L, Table 1). Interestingly, there were no samples with TSH levels between 30-50 mIU/L, and therefore no impact from the revised cut-off for direct clinical referral. Samples were collected at a median age of 3 days (range 2-6) and clinical notification occurred at 9 days (range 5-14 days). The majority of cases were found to have thyroid dysgenesis (72%, athyreosis or an ectopic gland) and most had low serum thyroxine at the time of clinical review (62%, either free T4 <10 pmol/L or total T4 <55 nmol/L). All infants, excluding one with transient CHT due to maternal Grave's and anti-thyroid medication, received thyroxine replacement, which commenced at a median of 10 days (6-44 days).

Mild TSH elevation

Of 44 infants with mild TSH elevation on their initial bloodspot (15-30 mIU/L), 15 were diagnosed with CHT (Fig. 3; 15/44, PPV 34%). Following discussion with their lead maternity carer, four infants had possible signs of hypothyroidism (such as jaundice and poor weight gain). Although TSH

was below the usual threshold for direct referral to a paediatric endocrinologist (18-29 mIU/L, all <30 mIU/L), these four infants were directly referred and were all confirmed to have mild CHT. A second bloodspot was collected from the remaining infants, where the reduced TSH cut-off (8 mIU/L) led to 7 extra clinical referrals, including 6 cases of mild CHT that would previously have been missed (Table 2). Thus, the lower cut-off applied to second samples led to a 15% increase in CHT cases detected (47/41), at the cost of minimal anxiety to families of healthy infants as just one infant without CHT was referred for clinical assessment.

Second samples were collected at a median age of 15 days (range 3-48 days), and notification occurred at a median of 20 days (range 9-52 days, Table 1). Despite the longer duration to clinical assessment, most CHT cases within this group displayed a pattern of compensated hypothyroidism with serum thyroxine levels within the normal range (86%, Table 1). This included two cases where collection of the second bloodspot was delayed beyond one month of age, and where clinical assessment subsequently occurred on days 49 and 52 (cases 3 and 4, Table 2). Both cases with low levels of serum thyroxine at clinical assessment followed initial screening TSH levels of ≥20 mIU/L (23 and 27 mIU/L blood, with clinical review and serum thyroid function assessed on days 11 and 15). In contrast to those who met criteria for direct referral, almost half of CHT was due to dyshormonogenesis (47%, Table 1). One infant with an *in situ* gland on ultrasound was observed off treatment at the request of his parents despite a low initial serum free T4 (8.7 pmol/L), and was found to have transient disease of unknown aetiology. All others diagnosed with CHT were treated with thyroxine, which commenced at a median age of 24 days (range 11-52 days, Table 1).

Low-birth-weight infants

In addition, there were 8 low-birth-weight infants (all NICU in-patients) with elevated TSH on their final screening sample (>8 mIU/L blood). Five were confirmed to have mild biochemical hypothyroidism (all had elevated serum TSH, with normal free T4 in 5 and borderline low in 3 cases).

Imaging was performed on 3 infants, and all found to have eutopic glands. Four infants commenced thyroxine replacement and one was monitored off treatment.

Missed case

We are aware of one case of CHT missed by newborn screening, which occurred in a term infant (birth weight 3150 g). Bloodspot TSH level on day 3 was 8 mIU/L, which is the 99.5th centile for appropriately timed samples within our population and well below screening cutoff, however the baby presented clinically with prolonged jaundice and was found to have elevated TSH on day 17 (serum TSH 28 mIU/L, free T4 28 pmol/L). There was no history of either iodine exposure or maternal thyroid disease. A diagnosis of dyshormonogenesis was made following scintiscan, and the infant commenced thyroxine replacement.

Screening thresholds and PPV

Given the lack of impact observed from our revised threshold for direct referral, we modeled the impact of lower cut-offs within our population (Table 3). Over the 2-year time period studied, a lower direct referral threshold of TSH ≥25 mIU/L would have led to 5 extra direct referrals (37/32, a 16% increase) and allowed earlier detection of 5 infants with CHT. The PPV of screening TSH levels between 25-29 mIU/L was 100%. If the referral threshold were reduced to TSH ≥20 mIU/L, there would have been 14 extra early referrals (46/32, a 44% increase), of whom 10 would have been cases of CHT. The PPV of screening TSH levels between 20-24 mIU/L was 55%, and 17% for TSH levels 15-19 mIU/L.

DISCUSSION

The revised New Zealand newborn screening algorithm led to a 15% increase in the number of infants diagnosed with CHT, achieved with a minimal increase in clinical workload and anxiety to families of healthy infants. Importantly, all of the observed benefits came from a small reduction in the TSH cut-off applied to second (repeat) screening tests performed in infants with mild elevation on their first sample. In contrast, a reduction in the TSH cut-off for the first screening sample would be anticipated to lead to a dramatic increase in the number of repeat samples and diagnostic evaluations [7, 8], and is a less efficient way to increase detection of mild CHT.

The primary justification of newborn screening for CHT is to prevent cognitive impairment by rapid detection of affected children. Long-term data from New Zealand has demonstrated that children with CHT picked up by newborn screening achieve the same intellectual outcomes as their unaffected siblings [3]. Conversely, approximately 25% of those with permanent clinically diagnosed CHT experienced overt disability (demonstrated either by low IQ scores or the need for special schooling) prior to the advent of newborn screening in the United Kingdom [10, 11]. These were predominantly children with severe disease, as evidenced by the low reported incidence of CHT (1:6500) [10]. What is less clear is whether infants with mild (and often transient) CHT also benefit from early detection and treatment. Cost-benefit analyses are based on the prevention of severe developmental delay and should not be extrapolated to the detection of increasingly milder cases [1]. There is most likely a continuous spectrum of intellectual effects from CHT – from severe to negligible – and outcome data for mild, subclinical, and transient CHT is urgently needed.

It is clear that lower TSH cut-offs generate a dramatic increase in false positive tests and further intervention in healthy infants. Mengreli et al. reported a 10-fold increase in false positive samples when blood spot TSH cut-offs were decreased from 20 to 10 mIU/L [7], and Langham et al. reported a four-fold increase in second samples following a reduction in threshold from 10 to 6 mIU/L [8].

Positive screening tests cause significant anxiety to parents of healthy newborn infants, which may persist even after good health is confirmed on follow-up testing [12]. Other harms include the direct health costs of additional recalls, diagnostic tests, increased laboratory and clinical workload, as well desensitization of health professionals (which may impact their response to severe cases of CHT). In view of these potential harms, coupled with unclear treatment benefit, our program opted not to decrease the overall TSH screening cut-off.

Like many screening programs, New Zealand utilises a 2-tier system whereby infants with greatly elevated TSH are directly referred to a paediatrician, but those with mild or borderline elevation are asked to provide a second screening sample. Infants in the first group have a high likelihood of severe CHT, where early diagnosis and rapid normalization of T4 offer the best chance of a normal intellectual outcome [13]. In contrast, infants in the second group are more likely to have mild CHT or to be healthy with a false-positive result. As expected, we found that the group of infants with CHT who had been directly referred had more severe disease, both structurally and biochemically. In our population, collection of a second bloodspot delays the diagnosis of CHT by nearly 2 weeks. This is due to a combination of individual and systemic factors, with the declining frequency of the postal service in New Zealand being of particular concern. Individual factors were at play in the two cases where the diagnosis of CHT was markedly delayed, namely bloodspot misplacement by maternity carer and difficulty contacting family for follow-up. Fortunately, both infants had mild disease and serum free T4 levels that remained within the normal range. Nevertheless, delayed collection of a second sample puts infants at risk of a prolonged period of early hypothyroidism. Local efforts to improve collection times for second samples include education of maternity carers and the use of a computer application to send text message reminders to maternity carers when second samples are delayed (in addition to mailed letters).

Unexpectedly, we observed no benefit from a moderate decrease in the TSH threshold for direct referral. This occurred as there were no infants with screening TSH levels of 30-50 mIU/L over the 2-year period studied. We speculate that this may reflect a bimodal distribution of TSH values in infants with CHT, separating those with severe disease and milder forms of CHT. Furthermore, the PPV of CHT following direct referral at 30 mIU/L was 100%, and remained high even when we modeled the impact of a further decrease to TSH ≥20 mIU/L. Of note, this lower threshold for direct referral would have led to direct referral of all cases with low serum T4, and automatic (rather than discretionary) early referral of nearly all infants noted to have possible hypothyroid symptoms at the time of notification. In general, earlier diagnosis (and lesser need for interim tests) is associated with reduced parental anxiety when children are diagnosed with metabolic diseases on screening [14, 15]. Overall, our data argue that a further reduction in the TSH threshold for direct referral would be beneficial within our population.

Over the two-year period, we were aware of one missed case of mild CHT. This occurred in a term infant with a screening TSH level well below the cut-off for our program or for almost all international programs [3]. Within our population, we estimate that a cut-off low enough to have detected this case would also result in an unacceptably high (14-fold) increase in repeat blood spots per year. Serum T4 was not decreased at assessment, so that a combined TSH and T4 test strategy would not have helped identify this case. Although New Zealand does not have a formal surveillance system for missed CHT, it is a relatively small country where there are strong links between the NMSP and clinical services as well as between paediatric endocrinologists nationally. Thus, it is reasonable to expect such cases to be reported to the NMSP. Prior to the introduction of a specific low-birth-weight protocol of routine repeat samples, most missed cases (1-2 per year) occurred in preterm infants, where the rise in TSH can be delayed secondary to immaturity of the hypothalamo-pituitary axis [16]. To the best of our knowledge, missed cases are now very rare and most often associated with known risk factors (e.g. twin birth).

The major limitation of our data is the relatively short time period studied (24 months) and consequent small number of CHT cases. This is the most likely explanation for the lack of benefit seen following reduction in the TSH threshold for direct referral. The NMSP will continue to monitor the impact of this and any further changes. Population differences, variable sample times, and use of different assays may all limit wider applicability of our data. Program comparison is further confounded by inconsistent clinical definitions of CHT, and the fact that the normal biochemical range for thyroid function in healthy infants is poorly defined [17,18, 19].

The strengths of our study include the fact that we examined a complete national data set, with a clear protocol for paediatric referral followed by case notification back to the NMSP. From this, we know that all 6 of the additional cases identified by the reduced cut-off for second samples were mild and had elevated serum TSH coupled with normal serum free T4. Whilst it is not possible to quantify the benefit of screening versus clinical detection for these infants, at least 2 cases (with ectopic glands) have permanent disease for which lifelong thyroxine replacement will be required.

Overall, we have shown improved performance of the New Zealand national newborn screening program for CHT, through a small reduction in the TSH cut-off applied to second samples. Over 2 years, this led to the detection of a number of cases that would previously have been missed, with a minimal increase in either clinical workload or anxiety for families of healthy infants. Although we had anticipated that a reduction in the TSH threshold for direct referral would also lead to earlier diagnosis in some infants, this did not eventuate. As a result of this study, the New Zealand screening programme has further reduced the TSH threshold for direct notification. It is also clear that further long-term data on infants with mild, transient, and subclinical hypothyroidism are urgently needed to inform screening policy.

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Figure Legends

Figure 1. Newborn screening algorithm for congenital hypothyroidism (CHT) in New Zealand in 1997-2012. All TSH concentrations are whole-blood measurements.

Figure 2. Newborn screening protocol for congenital hypothyroidism (CHT) in New Zealand from 2013. All TSH concentrations are whole-blood measurements. *TSH cutoff is ≥8 mIU/L for samples collected from babies older than 14 days.

Figure 3. Outcomes of newborn screening for congenital hypothyroidism (CHT) in New Zealand in 2013-2014. LBW, low-birth-weight infants. All TSH concentrations are whole-blood measurements. *Includes 30 unsuitable samples (i.e. collected too early, <46 hours of age) where TSH was above threshold (≥ 15 mIU/L), and subsequently normal on an adequate sample. †One infant with a normal screen was consequently diagnosed with CHT.

Table 1. Demography and clinical assessment of congenital hypothyroidism cases that were either directly notified (TSH >30 mIU/L) or notified following a 2nd screening sample (TSH 15-30 mIU/L). Data excludes the 5 NICU cases identified by following the repeat screening algorithm in low-birth-weight infants. All TSH concentrations are whole-blood measurements. Birth weight and gestational age data are means ± standard deviations; where appropriate, other data are medians and ranges.

		All	Directly notified	Notified after 2nd sample	P value
Cases		47	32	15	
Sex ratio (females)		27 (57%)	18 (56%)	9 (60%)	0.81
Birth weight (kg)		3.46 ± 0.58	3.56 ± 0.48	3.25 ± 0.72	0.08
Gestation (weeks)		39.4 ± 1.7	39.8 ± 1.6	38.6 ± 1.8	0.024
TSH (mIU/L)		95 (15–354)	143 (62–354)	22 (15–29)	<0.001
Age at final screening sample (days)		3 (2–48)	3 (2–6)	15 (3–48)	<0.001
Age at notification (days)		10 (5–52)	9 (5–14)	20 (9–52)	<0.001
Age commenced treatment (days)		10 (6–52)	10 (6–44)	24 (11–52)	<0.001
Laboratory turnaround (days)		1 (0–5)	1 (0–5)	1 (1–5)	0.51
Low free T4 at clinical review[a]		20/43 (47%)	18/29 (62%)	2/14 (14%)	0.004
Aetiology	Agenesis	7 (15%)	7 (22%)	0	0.015[b]
	Dyshormonogenesis	12 (26%)	5 (16%)	7 (47%)	

	Ectopic gland	22 (47%)	16 (50%)	6 (40%)
	Other or unknown	6 (13%)	4 (13%)	2 (13%)

[a] Where known, defined as serum free T4 <10 pmol/L or total T4 <55 nmol/L at paediatric review (pre-treatment).

[b] Comparing the distribution of the 3 most common aetiologies.

Table 2. Summary of congenital hypothyroidism cases detected that would previously have been missed, i.e. second sample TSH 8-15 mIU/L blood. DH, dyshormonogenesis; EG, ectopic gland; n/a, not available as serum thyroid function tests were not performed prior to thyroxine replacement.

	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**	**Case 6**
1st sample TSH (mIU/L blood)	24	20	28	26	15	18
2nd sample TSH (mIU/L blood)	10	14	11	12	12	10
Age at clinical notification (days)	10	26	45	51	22	23
Serum FT4 (pmol/L) (normal range 10-40)	20	13	n/a	13	16	14
Serum TSH (mIU/L) (normal range 0.4-16)	43	22	n/a	16	34	16
Aetiology	DH	DH	EG	EG	DH	DH
Age at start of treatment (days)	11	34	49	52	36	28

Table 3. Outcomes following a mildly elevated bloodspot TSH and the positive predictive value (PPV) of congenital hypothyroidism (CHT) at different TSH ranges. The total population is all appropriately timed New Zealand newborn screening bloodspot samples, 2013-2014.

Screening TSH level (mIU/L blood)	**Total number of infants**	**Infants with CHT**	**Healthy infants (no CHT)**	**PPV**
≥30	32	32	0	100%
25-29	5	5	0	100%
20-24	9	5	4	55%
15-19	30	5	25	17%