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Research Article

Congenital Hypothyroidism: An Audit and Study of Different Cord Blood Screening TSH Values in a Tertiary Medical Centre in Malaysia

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Mothers are often discharged within 24 hours in most Asian countries. Therefore, our screening programs for congenital hypothyroidism (CH) must consider the value of cord blood TSH. Our objectives were to compare the incidence of CH, positive predictive values, and recall rates using different cord blood TSH values. We also reviewed the results of the second-screening program for premature babies. 99.7% (n = 25,757) of all newborns were screened from 1st January 2009 to 31st December 2013. Babies with cord blood TSH > 25 mIU/L or 20–25 mIU/L and FT4 < 20 pmol/L were recalled for a repeat venous TSH and FT4 on days 3–5 of life to confirm CH. Twenty-two babies were confirmed to have CH, an incidence of 1:1170. Five were premature. Eleven term babies had cord blood TSH > 30 mIU/L and six had values 25.1–30 mIU/L. Lowering the recall cut-off value to 20 mIU/L would double the recall rate from 0.63% (n = 163) to 1.3% (n = 340) with no additional cases detected, whereas using 30 mIU/L would have missed 35% of cases. The incidence of CH was similar, 1:1515, when using either cut-off 20 mIU/L or cut-off 25 mIU/L but lower, 1:2380, when using 30 mIU/L. We recommend the screening cord blood TSH cut-off should be 25 mIU/L and screening for premature babies should be continued.

1. Introduction

Most developed countries offer universal newborn thyroid screening because while CH is common and easily treatable, early symptoms or signs are often absent [1–6]. When clinical manifestations are evident there is already irreversible cognitive impairment, hence the importance of prompt recognition and adequate treatment [1–3, 7–12].

Although there are universal CH screening guidelines, there are variations in screening strategies worldwide with regard to approach and timing [1, 7]. A primary TSH strategy is used in most countries with the chief objective being to detect primary CH. Some programs also measure T4 levels, for example, in the United States, Israel, Netherlands, and Japan [1, 7, 9]. Over the last decade, several newborn screening programs have reported that the incidence of CH has increased from 1:4000 to 1:2000, and lower TSH cut-offs appear to be the leading factor for this trend [1, 7, 9, 10, 13–15]. With lower TSH cut-offs, milder forms of CH, which could be transient, have been detected and also potentially more false positives, which could give rise to increased economic and labor burden [7, 9]. When the TSH cut-off was lowered from a range of >20–25 mIU/L to 6–10 mIU/L on a repeated 2nd screening, screening programs reported a doubling of the incidence of CH in Western Australia, Lombardy (Italy), North England, Greece, Quebec, and Brazil [7].

Besides approach, the timing of sample collection is also an important consideration. In most developed countries,

blood samples are captured on filter paper and are obtained after 24 hours of life [1, 7, 9]. The ideal collection is between days 3 and 5 of life because a surge in neonatal TSH, and consequently T4, occurs within minutes of birth and subsides to baseline over the next 24–72 hours [1–3, 7, 9, 16–18]. Hence, a 2nd screening is recommended if the specimen was collected within 24 hours of life to reduce the number of false positives [1–3, 7, 9].

However, in many developing Asian countries including Malaysia, mothers and their infants are often discharged from hospital within 24 hours of delivery and would return to their rural hometowns [10, 11, 19]. Therefore we should consider the value of cord blood TSH for screening rather than the more ideal use of TSH at 72 hours after birth. Information about the incidence, positive predictive value, detection, and recall rates using different cord blood TSH cut-off values would hence be important to improve our screening programs within our resources and local context. It is also practical in Malaysia as there is already an established local screening program for glucose-6-phosphate dehydrogenase (G6PD) deficiency using cord blood [10, 11, 20].

Screening for CH using cord blood TSH was started in University Malaya Medical Centre (UMMC), a tertiary medical centre in Malaysia, since August 1987. This was followed by a nationwide stepwise screening program for all babies delivered in the public hospitals [10]. In 2012, a second-screening program in UMMC involving venous TSH and fT4 was initiated for premature babies after their first week of life, as these babies may present with delayed TSH rise.

2. Methods

This study is descriptive and retrospective in nature. An audit of the newborn screening program in UMMC over a five-year period from 1st January 2009 to 31st December 2013 was performed. The total number of live births was obtained from the hospital's annual birth delivery book. Details of babies screened for CH during this period were obtained from the CH database of the paediatric endocrine clinic and medical records of babies with confirmed CH were retrospectively reviewed.

All live newborns had 3 mL of their cord blood taken in plain tubes and sent to the laboratory, where at least 100 μL of serum was obtained. The serum was assayed for TSH using an automated immune chemiluminescence assay system (Siemens). The functional sensitivity for TSH was 0.008 mIU/L, and analytical sensitivity for FT4 was 1.3 pmol/L. The results were stored in CH database and managed by the same medical laboratory technologist throughout the study period. The same technologist did the recall of patients and tracing of repeat venous samples. All babies with CH were followed up by the same consultant and her team.

The following cord blood TSH values were considered abnormal and were recalled for confirmation of CH with a repeat venous sample of TSH and FT4 at days 3 to 5 of life:

(i) cord blood TSH > 25 mIU/L or

(ii) cord blood TSH 20–25 mIU/L and cord blood FT4 < 20 pmol/L.

From 2012, premature babies of less than 37-week gestation were screened for CH via neonatal cord blood TSH with a second screening of weekly serum TSH and FT4 for 4 weeks.

Babies were confirmed to have CH and started on L-thyroxine if the repeat venous TSH was >20 mIU/L or the venous TSH was >10 mIU/L and the FT4 < 20 pmol/L after day 3 of life.

Babies born to foreigners and babies born before arrival at UMMC were excluded from this study. Babies who were confirmed to have CH received treatment with L-thyroxine (10–15 mcg/kg/day) as soon as the diagnosis was made and were followed up monthly in the first year to ensure their TSH was less than 5 mIU/L, preferably between 0.5 and 2.5 mIU/L [2, 7], and their FT4 was in the upper normal reference range for their age. In the second year, they were seen 2-3 monthly until they were 3 years old, when L-thyroxine was temporarily stopped for 4–6 weeks followed by a technetium thyroid scan. On the day prior to the thyroid scan, blood tests for TSH and FT4 were repeated to determine if there was an increase in TSH > 8 mIU/L and a fall in FT4 below the normal reference range. L-thyroxine would be resumed if there was a rise in TSH despite the presence of a normal thyroid gland as seen on the thyroid scan.

In this study our objectives were to compare the incidence and positive predictive values and recall rates using different cut-off cord blood TSH values of 20 mIU/L, 25 mIU/L, and 30 mIU/L. We also studied the results of the second screening for premature babies and reviewed the profiles of all infants diagnosed with CH with respect to their cord blood TSH and repeat venous TSH and FT4 and treatment and thyroid scan results.

3. Results

A total of 25,757 (99.7%) out of 25,834 live newborns were screened during the 5-year period, from 1st January 2009 to 31st December 2013. This figure compares favourably with other developed countries, for example, Western Australia (99%) and Scotland (99.9%) [10].

Twenty-two babies were confirmed to have CH and were treated during this period. This gave an overall incidence of 1 in 1170, higher than that in previous local studies and other Asian countries [7, 10, 11]; see Table 1.

Of the 22 babies, five were premature and were detected to have CH by the 2nd-screening program. Of the 17 treated term babies, all had cord blood TSH > 25 mIU/L. The number of term babies confirmed with CH with respect to their cord blood TSH and FT4 values is summarised in Table 2.

Of the 17 term babies who were treated, four were no longer under our follow-up. All of the 13 babies who were still under our follow-up continued to receive L-thyroxine, except for one patient whose medication was stopped at 13 months of age when the TSH was very suppressed despite taking a very low dose of thyroxine. The thyroid function remained normal when L-thyroxine was discontinued. This particular patient had a cord blood TSH of 25.43 mIU/L and a repeat venous blood TSH of 26.39 mIU/L and FT4 of 16.2 pmol/L on day 5 of life. Six patients had their thyroid scan performed at 3 years of age. One patient had an absent (agenesis) thyroid gland, and

Table 1: Comparison of incidences of CH reported in Asian countries and from local studies in Malaysia.

Country	Total screened	Year	Cases detected	Incidence
Malaysia				
Harun F.	19281	1992	7	1:2754
Amar HSS	8950	1997	3	1:2985
Wu L. L.	11000	1995	3	1:3666
Mafauzy	12261	NA	4	1:3065
Wong S. L. J.*	25757	2014	22	1:1170
Thailand	647000	1992	430	1:3314
Philippines	577000	1996	48	1:3678
Hong Kong	65000	2003	27	1:5681
Laos	14000	2008	2	1:2047
China	10700000	2012	5227	1:2404

*Overall incidence including 5 premature babies detected by 2nd screening.

Table 2: Number of term babies with confirmed CH with respect to their cord blood TSH and FT4.

Cord blood TSH (mIU/L)	Number of confirmed CH cases ($n = 17$)
>30	11 (65%)
25.1–30	6 (35%)
20–25	0

another had a sublingual thyroid. The remaining four (66%) patients showed normal technetium thyroid uptake on their scans. Table 3 shows the clinical profiles of the term babies with confirmed CH.

The recall rate using a cord blood TSH cut-off of 25 mIU/L was 0.63% ($n = 163$). The lower cut-off of 20 mIU/L had a low positive predictive value; the recall rate would double to 1.3% ($n = 340$) but no additional cases would be detected. Although the majority, 65% ($n = 11$), of babies with CH had a cord blood TSH > 30 mIU, using this cut-off would have missed 35% ($n = 6$) of cases. The incidence of positive CH cases is the same, 1 in 1515, for both TSH cut-off values of either 25 or 20 mIU/L. However, the incidence is lower, 1 in 2341, if 30 mIU/L is used. Comparisons between different TSH cut-offs 20, 25, and 30 mIU/L are summarised in Table 4.

All premature babies who were detected to have CH by the second screening of their weekly TFT after the first week of life had normal cord blood TSH and would have been missed if the second screening was not carried out. These babies had a delayed TSH rise after their first week of life (see Table 5).

4. Discussion

The overall incidence of 1:1170 ($N = 25757$) newborns with CH reported in UMMC over a five-year period from 1st January 2009 to 31st December 2013 is much higher than the previously reported local prevalence of 1:3117, based on pooled data from four local studies (one from a public hospital and three from local university hospitals) collected between 1991 and 1997 [10, 11]. The incidence is also higher than in other Asian countries, which have reported a range from 1:2000 to 1:5000 [7]. Possible reasons for the higher incidence could be the result of enhanced detection of neonates with mild disease due to the lower screening cut-off TSH values use compared to other hospitals, higher successful recall rates (UMMC is located in an urban area as opposed to rural areas where there may be difficulties to contact the family), different population ethnic composition, environmental factors, and the 2nd screening of premature infants detecting those with delayed TSH rise. This is also consistent with worldwide reports of doubling of the incidence of CH with lowering of the screening TSH cut-off and changes in birth demographics [7]. Even if the premature babies were excluded, the incidence rate for term babies during this study period is still high at 1:1515.

The incidence of CH is similar, 1 in 1515, regardless of whether a lower cut-off 20 mIU/L is used instead of 25 mIU/L. However, there is a lower incidence, 1 in 2341, if a higher cut-off value 30 mIU/L is used. Lowering the cut-off value from 25 to 20 mIU/L would have doubled the recall rate from 0.63% ($n = 163$) to 1.3% ($n = 340$) with no additional cases detected for twice the extra workload. The majority (65%, $n = 11$) of babies with CH had a cord blood TSH > 30 mIU/L with a lower recall rate of 0.3% ($n = 84$). Hence, using this higher cut-off of 30 mIU/L may seem attractive in terms of cost and workload but it should not be recommended because a high percentage (35%, $n = 6$) of the cases would have been missed. The recall rate of 0.6% for a cut-off of >25 mIU/L is acceptable and is similar to other countries' screening programs that use a primary TSH approach (reported 0.03 to 0.8%) [1, 14, 19]. Primary TSH screening has been reported to have a false positive rate ranging from 0.65%, in a screening program that applies 25 mIU/L cut-off, to 2.6% in a program applying 18 mIU/L cut-off [9, 21]. In comparison, our false positive rate was slightly lower at 0.56% for the 25 mIU/L cut-off and 1.2% for the 20 mIU/L.

A retrospective review of our patients' records revealed that, of the seventeen term babies who were treated, four were no longer under our follow-up. We are unsure if they had defaulted on follow-up or had transferred care to another centre, as attempts to contact them failed. Of the remaining thirteen who were still under follow-up, one patient had transient CH. This patient is currently 2 years old and successfully stopped taking L-thyroxine at 13 months. As reevaluation of treatment and thyroid scan is routinely done only at the age of three years, when most thyroid hormone dependent brain development is complete, only six patients have had their thyroid scan performed. One scan was reported as absence (agenesis) of thyroid glands, another one showed a sublingual thyroid, and the remaining four (66%) scans were reported as normal (normal size, location, and uptake). An early thyroid scan at diagnosis during the neonatal period is not done routinely in hospitals in Malaysia because of limited resources.

Although it was not one of our objectives, it would be interesting to investigate further the aetiology of CH in our

Table 3: Clinical profile of term babies with confirmed CH on follow-up.

Number	Sex	Ethnicity	Cord blood TSH (mIU/L)	Venous blood at days 3–5		Current age (years)	Thyroid scan (performed at 3 years of age)	TFT results after 4 weeks' cessation of L-thyroxine at 3 years of age		Comment
				TSH (mIU/L)	FT4 (pmol/L)			TSH	FT4	
1	F	M	26.44	25.17	16.5	4	Normal	20.42	10.5	
2	F	M	101.09	39	14.9	5	Absent glands	193.7	7.2	
3	M	C	28.64	14.37	20.7	5	Normal	26.69	13.3	
4	M	M	167.4	259.5	8.4	3.5	Normal	7.4	23	
5	M	C	28.73	22.67	21	4	Normal	43.58	29.9	
6	F	M	362.2	150	13	3.5	Sublingual thyroid	521	4.5	
7	F	M	25.45	26.39	27.6	2	NA	NA		L-thyroxine stopped at 13 months of age
8	M	M	28	19.3	20	3	NA	NA		Down syndrome
9	F	C	30.69	34.78	15.3	2	NA	NA		
10	F	M	30.49	14.86	24	2	NA	NA		
11	F	M	360	377	9.3	1.5	NA	NA		
12	F	C	75.76	69.7	NA	1.5	NA	NA		Mild speech delay, widened AF
13	M	M	70.59	139.7	16.7	0.75	NA	NA		
14	F	I	96.73	58.1	16.8	5	—	—		Defaulted follow-up

Sex: M: male and F: female. Ethnicity: M: Malay and C: Chinese.
None of the patients were noted to have developmental delay except for patient number 12. All were still on L-thyroxine except for patient number 7.

Table 4: Comparison of different screening cut-off values.

Cord blood TSH cut-off (mIU/L)	Positive screened (recall rates) (n = 25757)	True positives (confirmed CH by repeated TFT at days 3–5)	False positives	Positive predictive value	Incidence	False positive rate
>30	84 (0.32%)	11	73	13%	1:2341	0.28%
>25	163 (0.63%)	17	146	10.6%	1:1515	0.56%
>20	340 (1.3%)	17	323	5%	1:1515	1.2%

patients. The commonest permanent cause of CH reported was dysgenesis of the thyroid gland; however dyshormonogenesis among the Asian population has recently been shown to be a significant cause of CH [3, 8, 13, 15, 22–26]. In our audit, 66% (n = 4) of our permanent CH patients had normal thyroid scans. All were restarted on thyroxine because of TSH rise >8 mIU/L after a month's trial of stopping medication at 3 years of age. The possible cause for this group of patients with normal scans was dyshormonogenesis. Mutations in the thyroid peroxidase (TPO) gene are known to be responsible for the majority of cases of CH with dyshormonogenetic glands [23, 25–27]. However, the number of patients is too small to draw any conclusions, and genetic studies have yet to be performed on these patients.

International guidelines recommend a second-screening specimen at 2 to 6 weeks of life for high risk groups, premature, LBW, VLBW, ill babies, or multiple births, as these babies may present with delayed TSH rise [1–3, 28, 29]. Possible reasons for the delayed TSH rise include immaturity of the hypothalamic-pituitary axis, medications such as dopamine or steroids, use of iodine for procedures, and unwell babies ("sick thyroid syndrome") [1–3, 28, 29]. For premature babies, serial screening should be considered at 2, 6, and 10 weeks of age or until they reach 1500 g or at discharge [1–3, 28, 29].

Table 5: Clinical profiles of premature babies with CH.

Patient	Gestation (weeks)	Birth weight (g)	Sex	Cord blood TSH (mIU/L)	TSH (mIU/L), FT4 (pmol/L) values at week of diagnosis	Current age (months)	Current dose of L-thyroxine (mcg/day)	Current status*
1	28	750	M	10.52	TSH 42, FT4 8.6 at week 2	15	25	Normal development
2	29	1100	M	10.2	TSH 15.8, FT4 17 at week 2	11	25	Normal development
3	24	595	F	5.25	TSH 105, FT4 6.3 at week 4	24	25 alt 37.5	Normal development
4	34	1180	F	9.07	TSH 138.9, FT4 5.5 at week 2	16	37.5	Speech delay
5	32	940	M	1.38	TSH 25.27, FT4 17.3 at week 2	34	25	Normal

*All are still on thyroxine.

However, due to limited resources and the cost, this is not done routinely in most hospitals in Malaysia. In UMMC, a second-screening program for premature babies (gestation less than 37 weeks) has been in place since 2012, where venous TFT (both FT4 and TSH) is done every week until 4 weeks of life. To date, there have been five premature babies diagnosed with CH, and their birth weights were all less than 1500 g. All except one had normal cord blood TSH values (<25 mIU/L) and presented later with delayed TSH rise after 1 week of life. From our review of clinic notes, all the premature babies were confirmed to have CH and are still on L-thyroxine and under regular follow-up. No thyroid scan has been done yet as they are currently still younger than 3 years of age. One patient has speech delay, which could be due to a complication of both prematurity and hypothyroidism.

Our findings of five premature babies with permanent CH who had significant delayed TSH rise support the existing guidelines that a 2nd screening for premature babies should be considered in Malaysia [1, 28, 29]. However, the sample size is small and, for it to be implemented, further studies to analyse the cost-effectiveness and long term follow-up for this group of babies are needed.

5. Conclusion

The overall incidence of CH in UMMC from 1st January 2009 to 31st December 2013 was 1:1170 (n = 25,757) newborns, which is nearly three times higher than previously reported in Malaysia. Lowering the cut-off for cord blood TSH from 25 to 20 mIU/L would have doubled the recall rate and found no additional babies with CH. Using a cut-off of >30 mIU/L had a lower recall rate but would have missed 35% of cases. Based on this, we recommend that the screening cord blood TSH cut-off should be 25 mIU/L. Screening of cord blood FT4 for borderline TSH 20–25 mIU/L to detect CH may be discontinued as it has a low positive predictive value. Screening for premature babies should continue with weekly TFT from the 2nd week of life.

Abbreviations

CH: Congenital hypothyroidism
TSH: Thyroid stimulating hormone
FT4: Free T4
TFT: Thyroid function test
LBW: Low birth weight
VLBW: Very low birth weight
UMMC: University Malaya Medical Centre.

Conflict of Interests

The authors declare that they have no conflict of interests.

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