

Recall rate and incidence of congenital hypothyroidism: A 5-year experience of hospital-based study in Bahrain.

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Abstract

Background: Different neonatal screening programs for congenital hypothyroidism (CH) have been implemented to prevent its devastating effects on mental development. High recall rate and false positive results subject families to undue stress and impose financial burdens on health care expenditures. **Objective:** to investigate the CH recall rate and establish an optimum cord blood thyroid-stimulating hormone (CBTSH) level for CH diagnosis.

Methods: retrospective cross-sectional study was conducted in Bahrain Defense Force hospital from Jan 2012 to Dec 2016. CBTSH and back-up free thyroxine (T4) results from all newborn infants born during this period were analyzed. All of the infants with CBTSH >37.5 µIU/ml were recalled for confirmatory tests.

Results: Out of 20,885 newborns, 413 infants were recalled (recall rate 1.98%). CH incidence was 1:1489, mean CBTSH was 99.5 µIU/ml (95% confidence interval (CI) 98.7-100.3 µIU/ml), and mean free T4 was 9.1 pmol/l (95% CI, 6.64-11.57 pmol/l). A receiver operating characteristic (ROC) curve identified the new CBTSH cutoff value as 93 µIU/ml.

Conclusion: Our study supports setting a higher CBTSH cutoff value based on our population findings and recommends both CBTSH and simultaneous free cord T4 measurements as the ideal screening approach.

Keywords: Infants, Health care, Stress.

Abbreviations: CH: Congenital Hypothyroidism; CBTSH: Cord Blood Thyrotropin Stimulating Hormone; ROC: Receiver-Operating Characteristic

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Introduction

Congenital hypothyroidism (CH) is one of the most common preventable causes of intellectual disability. It affects 1:2000 to 1:4000 new-born infants worldwide [1,2]. The clinical manifestations are usually subtle or not present at birth [3]. Different neonatal screening programs for CH have been implemented in both developed and some developing countries. It is estimated that only 1/4 of the worldwide birth population undergo screening for CH [4,5].

In many countries, different mass screening programs are performed for early diagnosis and treatment of CH [6], yet most have encountered problems such as high recall rate and therefore, more substantial numbers of false-positive results are found, which carry a risk for unjustified anxiety and psychological harm in families. On the other hand, fewer false positive results increase physicians'

and parents' trust, reduces families' psychological stress, efficiently organize the medical staff members' workload and reduce expenses by minimizing unnecessarily repeated laboratory tests [7,8]. In this study, we determined both CH incidence and recall rates based on our local neonatal population that was screened over the study period and redefined the cord blood thyrotropin-stimulating hormone (CBTSH) cut-off levels for identifying neonates at risk of CH.

Materials and Methods

Materials and Subjects

This is a retrospective cross-sectional study that was carried out from January 2012 to December 2016 in Bahrain Defense Force Hospital. All inborn deliveries conducted during this period were part of the study. Primary CBTSH with backup T4 measurements were assayed on single specimens using the electrochemiluminescence

immunoassay “ECLIA” by Cobase immunoassay analyzer (ROCHE Diagnostics, Germany) with a measurement range of 0.005 to 100 µIU/ml and 0.3 to 100 pmol/l for TSH and free T4, respectively. For confirmation, infants were recalled if cord blood TSH was >37.5 µIU/ml, and serum TSH and free T4 measurements were obtained at an average of five days after birth. Thyroid scans using Tc-99m were requested to determine the underlying etiology. Clinical data were obtained for all positive cases included sex, gestational age, nationality, type of delivery and single or multiple gestations.

Statistical Methods

Statistical data were analyzed using SPSS software version 19.0. Descriptive statistics were performed using the calculation of frequency, percentages, mean and standard deviation (SD). Sample characteristics were summarized using mean ± SD for numerical data and frequency and percentages for categorical data. The CBTSH values of all confirmed cases of CH and false positive cases were pooled to generate a receiver operating characteristic (ROC) curve using MedCalc statistical software to determine appropriate CBTSH cutoff value for CH diagnosis. The hospital ethics committee approval was obtained.

Results

The total number of babies born at Bahrain Defense Force Hospital during the study period was 20,855 newborn infants, of which 413 (1.98%) were identified to be at risk (Table 1) as they had CBTSH >37.5 µIU/ml. Out of that 78.5% were Bahraini and 237 infants (57.7%) were males. Term, pre-term, post-term and extremely pre-term infants accounted for 74.1%, 24.7%, 0.7% and 0.5%, respectively. Cesarean section was the mode of delivery of 57.1% infants compared to 36.6% spontaneous vaginal delivery (SVD) and 6.3% assisted vaginal delivery. (5.3%) were part of multiple gestations. In populations found to be at risk, mean CBTSH and T4 were 55.70 ± 18.53 µIU/mL and 23.51 ± 9.79 pmol/L, respectively (Figure 1).

Table 2 shows the number of neonates screened annually and number of true positive and false positive cases. No false negative cases were observed in this study and the overall incidence of congenital hypothyroidism during the study period was 1:1489 (Figure 2).

Table 3 demonstrates CBTSH and cord blood free T4 results. Thyroid ultrasound, scintigraphy reports of all 14 confirmed cases of primary hypothyroidism.

Table 4 demonstrates the CBTSH distribution. There were 20,442 (98.02%) negative tests (CBTSH <37.5 µIU/mL) and 413 positive tests (CBTSH >37.5 µIU/ml) accounting for 1.98%, which was the recall rate.

Figure 3 and Table 5 shows the ROC curve created from plotting the true positive results (sensitivity) against the false positive results (1-Specificity) [9,10]. CBTSH of 93 mU/l as the appropriate detection cutoff for the diagnosing

Table 1. Descriptive distribution of all screened positive cases

Variable	Frequency	Percentage	Range
Gestational Age			
Preterm	102	24.70%	-
Post-term	3	0.70%	-
Extreme Preterm	2	0.50%	-
Term	306	74.10%	-
Gender			
Male	237	57.60%	-
Female	176	42.60%	-
Nationality			
Bahraini	324	78.50%	-
Non-Bahraini	89	21.50%	-
Delivery type			
SVD	151	36.60%	-
Caesarean	236	57.10%	-
Assisted Vaginal Delivery	26	6.30%	-
No. of Gestation			
Singleton	392	94.70%	-
Multiple	21	5.30%	-
Cord TSH (Mean ± SD)	55.70 ± 18.53	-	37.66-100
T4 (Mean ± SD)	23.51 ± 9.79	-	3.76-85.70

CH with a sensitivity of 100% (95% CI, 76.8%-100%) and a specificity of 95% (95% CI, 92.4%-96.9%).

Discussion

The use of CBTSH as a screening tool for CH has been validated in numerous studies [11]. CBTSH values have been evaluated and compared with filter paper samples obtained via heel prick [12]. Hardy et al. [13] found CBTSH to be more sensitive than cord blood free T4 screening.

There are wide variations in screening strategies worldwide with regard to timing and methods of screening [14,15]. Primary TSH with backup T4 measurements is widely used in Europe, Japan, Canada, Mexico and the United States. Some programs in North America, Israel and the Netherlands also use primary T4 measurements and both methods use heel prick samples at 2 to 5 days after birth [5,16,17].

The use of CBTSH as a screening tool in developing Asian countries provides an attractive alternative because of its simplicity and accessibility considering the obstetric practice in which the majority of mothers are discharged within 24 to 48 h after delivery [14,18,19].

By using a cutoff value of 37.5 µIU/ml in our hospital, we identified 413 infants at risk out of a total population of 20,855 infants. Fourteen infants in the population

Table 2. Population incidence of congenital hypothyroidism in Bahrain from 2012 to 2016

Year	No. of Neonates Screened	Total Positives	No. of True Positives (TP)	No. of False Positives (FP)	No. false Negatives (FN)	Population Incidence
2012	4013	87	3	84	0	1:1337
2013	4034	95	4	87	0	1:1008
2014	4245	95	4	91	0	1:1061
2015	4256	70	1	69	0	1:4256
2016	4307	70	2	68	0	1:2153
Total	20,855	413	14	399	0	1:1489

Table 3. Clinical data for 14 infants with thyroid abnormalities

Cases	Nationality	Gender	Cord blood TSH	Cord FreeT4	Ultrasound	TC99
1	Non-Bahraini	Female	100	10.04	Normal	N/A
2	Non-Bahraini	Female	100	7.23	Not visualizes	No uptake
3	Bahraini	Male	100	16.3	Enlarged thyroid	Increased uptake
4	Bahraini	Female	100	8.09	Not visualized	No uptake
5	Non-Bahraini	Male	100	6.83	Normal size	Increase uptake
6	Non-Bahraini	Male	100	8.34	N/A	Increased uptake
7	Non-Bahraini	Male	100	14.6	N/A	No uptake
8	Bahraini	Male	100	9.33	Enlarge thyroid	Increased uptake
9	Bahraini	Male	100	6.04	N/A	N/A
10	Non-Bahraini	Female	100	4.28	N/A	N/A
11	Bahraini	Male	94.21	9.96	Not visualized	No uptake
12	Bahraini	Male	100	6.18	Enlarged thyroid	Increased uptake
13	Non Bahraini	Female	100	6.73	N/A	N/A
14	Bahraini	Male	100	3.76	Not visualized	No uptake

Table 4. TSH distribution

CBTSH	Number of Cases	Percentage
TSH (<37.5)	20,442	98.02%
TSH (>37.5)	413	1.98%
Total	20,855	100.0%

Table 5. Criterion values and coordinates of the ROC curve

Criterion	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR
≥ 37.66	100.00	76.8-100.0	0.00	0.0-0.9	1.00	
>93.96	100.00	76.8-100.0	94.99	92.4-96.9	19.95	0.00
>99.1	92.86	66.1-99.8	95.74	93.3-97.5	21.79	0.075
>100	0.00	0.0-23.2	100.00	99.1-100.0		1.00

identified at risk were confirmed after repeat TSH and free T4 as being hypothyroid. An overall incidence of 1:1489, which was higher than the previously reported incidence of 1:2967 [20] and estimated worldwide incidence of 1:3000 [21], was similar to Najran province in Saudi Arabia (1:1400), Iran (1:1439) and 1:1500 in Ontario, Canada [22-24].

Recall rates in various programs around the world range from 0.01% to 13.3% [6]. Our study had a recall rate of 1.98% compared to 0.05%–0.3% found in other primary TSH screening programs [16,25].

The lowest TSH value detected in confirmed CH cases was 94 μ IU/ml, which is consistent with values from a

Swedish study (100 μ IU/ml) and from Najran province in Saudi Arabia (117 μ IU/ml) [26,27].

The ROC curve identified a new cutoff CBTSH value as 93 μ IU/ml. When used, it would improve the efficiency of the test and lead to less false positive cases, and hence lower recall rates, which in return will significantly improve the cost-effectiveness of this screening tool and minimize concerned parents' anxiety for whom their infants are identified as at risk [6,8].

Limitations

Study limitations included the retrospective design and use of primary TSH and backup free T4 measurements,

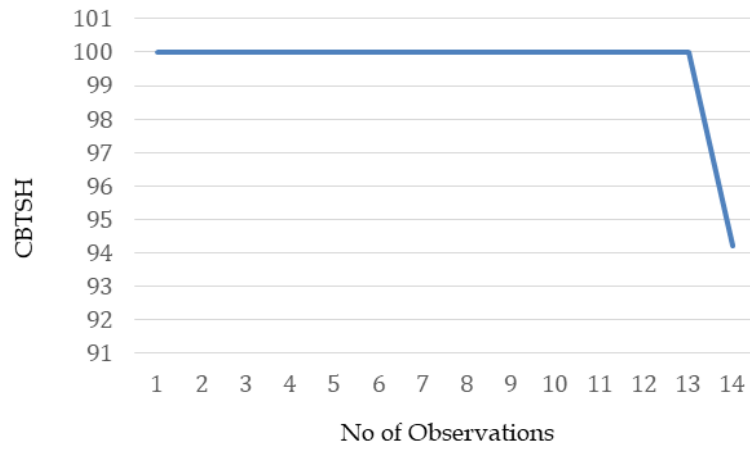


Figure 1. Frequency distribution of true positive of cord blood thyrotropin stimulating hormone ((CBTSH) n=14)

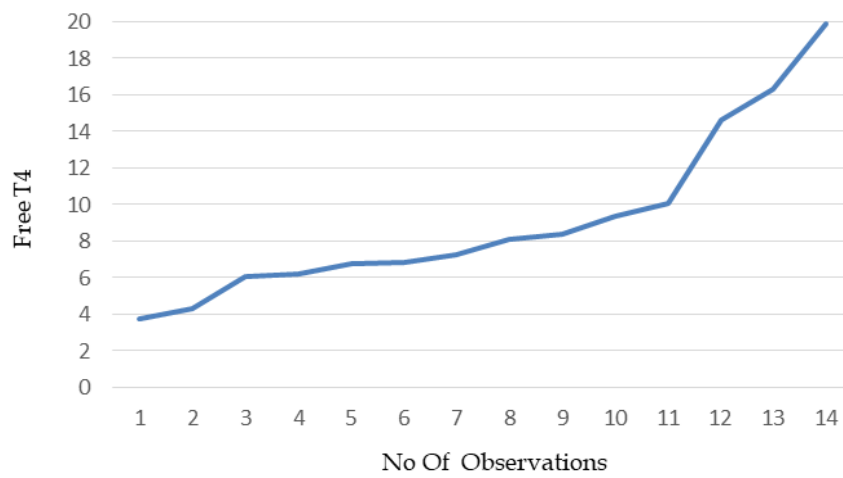


Figure 2. Frequency distribution of true positive free T4 in cord blood (n=14)

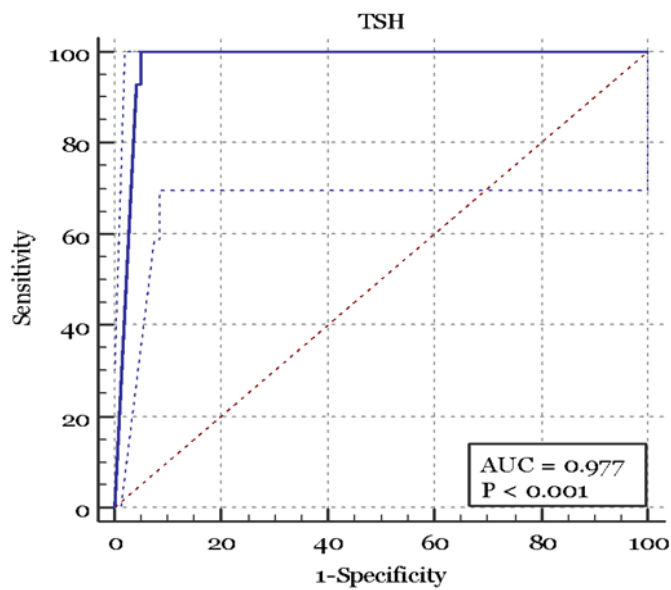


Figure 3. ROC curve of cord blood TSH

which may miss cases of central hypothyroidism and cases with delayed TSH elevation seen in low birth weight and very low birth weight infants (LBW and VLBW, respectively) and infants with thyroid-binding globulin (TBG) deficiency. An approach using simultaneous TSH and free T4 measurements seems to be the preferred ideal method to diagnose CH [16,28].

Conclusion

To date, there is no universal TSH cutoff point to screen for CH. Each country should collect enough data to determine a credible and feasible screening method and cutoff values aiming to achieve low false positive results and recall rate. CBTSH screening per se will detect neonates with primary CH, yet cases with central hypothyroidism and those with delayed TSH elevation can be missed. Our study supports setting higher CBTSH cut-off values based on our population findings and recommends simultaneous cord free T4 measurements as the ideal screening approach.

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