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Congenital hypothyroidism screening in neonates in an iodine deficient endemic region: A prospective study at a tertiary care centre in north India

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Abstract

Introduction: Congenital Hypothyroidism is one of the most common causes of preventable mental retardation with an estimated incidence of 1:2500-2800 live births in India. The need for neonatal screening for CH is essential as the majority of signs and symptoms are not exhibited in the neonatal period.

Aim: To use TSH values as a marker for screening for Congenital Hypothyroidism in neonates in an iodine deficient endemic region and to find normative values of Serum TSH for the study group.

Material and Methods: A prospective observational study was conducted over a period of 18 months. A total of 500 newborns who fulfilled inclusion criteria were enrolled. Umbilical Cord Blood samples (2ml from placental side) were taken for TSH values for all Term neonates with birth weight ≥ 2.5 Kgs whereas Serum TSH values at 48-72 hours of life were taken for Preterm (<37 completed weeks) and Low birth weight neonates. All babies who had a cord blood TSH value of >20 mIU/L were sampled again for TSH and T4 and if repeat TSH was >20 mIU/L and/or T4 < 10 mIU/L they were subjected for further examination and treatment if required.

Results: The mean cord blood TSH was 7.26 mIU/L in our study, with 7.28 mIU/L in term neonates and 6.94 mIU/L in preterm neonates. Nine babies had TSH values >20mIU/L in the initial screen but all were <20 mIU/L on repeat sampling. Hence none of the 500 neonates who were screened for CH in our study were detected to have congenital hypothyroidism. TSH values corresponding to the 5th, 10th, 25th, 50th, 75th and 95th percentile were 3.08, 4.71, 5.39, 13.18, 21.65 and 39.22 respectively. The babies born to mothers with hypothyroidism, had higher TSH values compared to those without risk factors.

Conclusion: In our study, none of the 500 newborns screened had congenital hypothyroidism. We observed that neonates born to mother with hypothyroidism had higher cord blood TSH which was statistically significant. According to our normogram, the 50th centile corresponded to 13.18 mIU/mL which is <20 mIU/mL while neonates above 75th centile had TSH values above 20 mIU/ml.

Keywords: Congenital hypothyroidism, TSH, newborn screening

Introduction

Thyroid hormone deficiency is one of the leading causes of preventable mental retardation [1]. The need for neonatal screening for CH is essential as the majority of signs and symptoms are not exhibited until

3 months of age due to residual thyroid function or transplacental passage of maternal thyroid hormone [2, 3]. The first screening study in India which included more than 1 lakh neonates was done by Indian Council of Medical Research (ICMR) National Task Force Team on Newborn screening at All India Institute of Medical Sciences (AIIMS), New Delhi from 2007-2012and an overall incidence of 1:1172 was seen with an incidence of 1:727 in South Indian population [4, 5].

In view of the serious consequences of delaying diagnosis and treatment for cases of congenital hypothyroidism and strong recommendations for newborn screening for the same, this study was planned using TSH values at birth to screen for congenital hypothyroidism. Himachal Pradesh (HP) state is a known endemic region to Iodine deficiency [6]. With iodine deficiency being a risk factor for transient congenital hypothyroidism, the normative TSH values for newborns in this region have also been studied. This would help in early detection and treatment of congenital hypothyroidism in newborns to realize their neurological potential and growth thus reducing the morbidity of preventable mental retardation and growth failure.

Materials and Methods

A prospective observational study was conducted in the Department of Paediatrics over a period of 18 months w.e.f. Jan 2020. A total of 500 newborn babies were included in the study as per inclusion and exclusion criteria mentioned below.

Inclusion criteria

1. All Term (37-42 weeks) neonates weighing 2.5Kgs or more delivered during the study period for cord blood sampling.
2. All preterm and Low Birth Weight (less than 2.5Kgs) with sample for Serum TSH at 48-72 Hrs.

Exclusion criteria

1. Babies requiring resuscitation (bag and mask >1min / cardio-pulmonary resuscitation).
2. Sick neonate.
3. Neonate with major congenital malformations.
4. Parents refusing to give consent.

Collection and processing of sample: Umbilical Cord Blood samples (2 ml from placental side) were taken for TSH values for all Term neonates with birth weight ≥ 2.5 Kgs whereas Serum TSH values taken between 48-72 hours of life were considered for Preterm (<37 completed weeks) and Low birth weight neonates i.e. neonates with birth weight < 2.5 Kgs (LBW). Gestational assessment for prematurity was done on the basis of LMP/EDD and ultrasound dating and was confirmed by Modified Ballard's scoring. TSH was determined using ADVIA Centaur CP Immunoassay System. All term neonates with Cord blood TSH> 20 mIU/L underwent repeat testing for T4 and TSH at 48-72 hours of life. All Preterm and LBW neonates with TSH> 40 mIU/L underwent repeat testing for TFT immediately, while those with TSH 20-40 mIU/L underwent repeat testing for TFT at 7-10 days of life. All neonates with repeat TSH value ≥ 20mIU/L within 2 weeks of life and/ or with low T4 (<10 μg/dL) were to be considered to have primary CH and initiated on treatment. Normal values considered were cord blood TSH < 20mIU/L, T4 >10μg/dL. The data collected was entered in SPSS (statistical package social sciences) VERSION 20 and Microsoft excel sheet. Categorical data was summarized using frequency distribution and proportions. Numerical data was summarized using mean and standard deviation. T-test and ANOVA test were used to find the significance difference of continuous variables. The P value <0.05 was considered significant. Informed and written consent (in the language they best understand) were taken from each subject before collecting data and blood sample. Only those individuals, whose parents

volunteered to participate in the study, were included and the data was kept confidential. The proposed study was undertaken after approval by Institutional Ethical Committee.

Results

A total of 500 neonates born during study period were enrolled with the aim of using TSH values as a marker for screening for Congenital Hypothyroidism in neonates in an iodine deficient endemic region.

Table 1: Baseline demographic data and TSH values of the study population

Category		Total Number	Percentage	TSH (MEAN) In µg/dL	TSH (SD)	P Value
Gender:	Male	245	49%	7.51	2.81	
	Female	255	51%	7.02	2.56	0.24
Gestational Age:	Preterm	34	6.8%	6.94	2.99	0.67
	Term	466	93.2%	7.28	2.53	
BWT:	AGA	433	86.6%	7.29	2.83	
	LGA	7	1.4%	8.57	2.69	0.032
	SGA	60	12%	6.92	2.39	
Mode of Delivery:	NVD	365	73%	7.13	2.43	
	LSCS	133	26.6%	7.66	2.91	0.024
	FORCEP	2	0.4%	4.50	2.12	

Table 1 shows the baseline demographic characteristics of the study population along with Mean TSH levels.
Mean TSH levels among the study subjects was 7.26±4.56.
Mean TSH level among AGA, LGA and SGA subjects was 7.29±2.83, 8.57±2.69 and 6.92±2.39 respectively with statistically significant difference.
Mean TSH level was found to be more among subjects delivered with LSCS (7.66) followed by NVD (7.13). Least TSH level was found among subjects delivered through forceps (4.50). When TSH level was compared using a nova test w.r.t. mode of delivery, it was found to be statistically significant as $p<0.05$.

Table 2: TSH values in 1st and 2nd samples of the study population

Category	Total Number	Percentage
TSH 1st Sample: <10mIU/L	410	82%
11-20	81	16.2%
21-30	7	1.4%
31-40	2	0.4%
Mean ± SD	7.26±4.56	
TSH 2ND Sample: <5mIU/L	6	66.6%
5-10	2	22.2%
10-20	1	11.2%
Mean ± SD	4.16±3.15	

TSH level <10, 11-20, 21-30 and 31-40 was found among 82%, 16.2%, 1.4% and 0.4% of the subjects respectively. Hence 9(1.8%) babies were screen positive with level of above 20 µIU/L at first sampling. Among the nine subjects with TSH>20 mIU/L, each one had TSH level <20 on analysis of their second sample. Hence none of the newborns in our study were found to have congenital hypothyroidism.

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Table 3: Distribution of TSH level according to percentile

Percentile	TSH Value	N	%
5th	3.08	91	18.2
10th	4.71	149	29.8
25th	5.39	146	29.2
50th	13.18	105	21
75th	21.65	8	1.6
95th	39.22	1	0.2

According to our normogram, the 50th centile corresponded to 13.18 mIU/mL which is <20 mIU/mL while all neonates above 75th centile had TSH values above 20 mIU/ml and required repeat sampling.

Table 4: Comparison of TSH according to antenatal risk factors

Variables	TSH		p value
	Mean	SD	
PIH			
Present	7.29	3.92	0.97
Absent	7.26	4.59	
Hypothyroidism			
Present	9.68	6.53	0.002*
Absent	7.10	3.99	
Gestational Diabetes			
Present	8.23	5.29	0.44
Absent	7.23	4.54	

*: statistically significant

The various risk factors in mothers included Hypothyroidism (6.2%), PIH (4.8%), Eclampsia (0.4%), Gestational diabetes (2.6%), Meconium stained amniotic fluid (5.8%), multiple pregnancy (4%), premature rupture of membranes (2%), nil (78.2%), others (0.8%). TSH values for neonates born to mothers with PIH, Hypothyroidism and Gestational diabetes were studied. TSH level was significantly higher in mothers with history of hypothyroidism with significant difference as p value was 0.002 (<0.05).

Discussion

Mean TSH levels among the study subjects was 7.26±4.56. Incidence of hypothyroidism among the 500 babies screened was nil.

Mean TSH level among AGA, LGA and SGA subjects showed a statistically significant difference. Seeralar *et al*. in their study revealed that there is no statistical significance between low birth weight and normal weight babies with respect to their TSH values [7].

Mean TSH level was also found to be significantly higher among subjects delivered with LSCS (7.66) followed by NVD (7.13). Least TSH level was found among subjects delivered through forceps (4.50). When TSH level was compared using anova test w.r.t. mode of delivery, it was found to be statistically significant as p<0.05.Similarly Ahmad *et al*. in their study reported that association was found between mode of delivery and congenital hypothyroidism. Out of 251 normal deliveries only one case and of 519 cesarean sections, two cases were found to be hypothyroid [8].

Seth A *et al*. in their study revealed elevated TSH level among forceps extraction as compared to C-section, which contradicts findings of current study [9]. Kumar S *et al*. in their study showed that newborns delivered by elective Caesarean Section had significantly lower mean levels of cord blood TSH as compared to those delivered by vaginal delivery or emergency lower segment cesarean section [3].

Mean TSH level among the study subjects was 7.26±4.56.Various cut-offs for TSH levels have been used in different studies, but it has been accepted to take cut-off of >20 μIU/mL for recall. Using this cut-off, only 9 (1.8%) babies were screened positive with level of above 20 mIU/L on first sampling in our study and underwent repeat testing.

Similarly, Kumar *et al*. in their study found a total of 14 babies out of 1272 (1.1%) babies which were subjected to retesting [3]. Manglik *et al*. in India also reported that 22 babies out of 1200 (1.8%) had TSH>20 mIU/Lwithin first 24 hrs which was same as ours [10]. Bhat *et al*. in their study found 35 babies out 3000 (1.1%) babies who had TSH>20 mIU/L in the first sample [11].

In contrast, Raj *et al*. in their study found 41 babies out of 430 (9.5%) babies who had TSH>20 mIU/L within first 24 h [12].

However none of the nine neonates who underwent repeat sampling turned out to have hypothyroidism. Hence overall incidence was nil among 500 subjects. Reported worldwide incidence is 1 in 4000. In India the incidence is 1:1172 with south India reporting an incidence around 1:727 [5].

Raj *et al*. in their study found 5 babies out of 41`babies who had an initial cord blood value >20 mIU/L to have CH in the subsequent tests and treated accordingly. The incidence in their study was 3:430 [12]. Bhat *et al*. in the study conducted by them observed that 8 newborns out of the 35 initially tested babies were labeled as CH with repeat TSH >20 mIU/L. The incidence in their study was 1:350 [11]. Kumar *et al*. in their study found 2 babies out of 14 babies initially tested to have CH with repeat TSH>20 mIU/L. The incidence in their study was 1:636 [3].

Ramya *et al*. in their study found 3 babies out of 2376 babies screened as cases of CH. The incidence in their study was 1.26:1000 [13]. Sharma *et al*. in their study which was conducted on 314 babies recalled 13 babies for retesting after initial screening. The incidence of hypothyroidism in their study was 7:314 [14]. In our study, none of the newborns screened had CH, which could be attributed to inadequate sample size. However we could conclude that the incidence was not higher than reported in other studies and that Himachal Pradesh being an endemic region for iodine deficiency did not lead to higher incidence of congenital hypothyroidism.

Percentiles of TSH

The distribution of TSH values in this study group of 500 neonates were 5^{th} percentile as 3.08, 10^{th} percentile as 4.71, 25^{th} percentile was 5.39, 50^{th} percentile as 13.18, 75^{th} percentile as 21.65, 95^{th} percentile as 39.22.

Bhatiya and Rajwaniya in their study found TSH values in terms of various percentiles. The observations were plotted according to the 3rd, 10th, 25th, 50th, 90th, 95th, and 97th percentile. The values of TSH corresponding to the above mentioned percentiles were 2.32, 4.05, 5.67, 7.5, 12, 20.63 and 30.88 respectively. Though our 50^{th} centile TSH values corresponded, retesting would be required above 75^{th} centile in our study and 95^{th} centile in their study [15].

Correlation of Antenatal risk factors with TSH values

TSH level was significantly higher in mothers with history of hypothyroidism. The mean TSH value in the neonates was found to be 9.68 with significant difference as $p<0.05$ in our study. Anjum A *et al*. in their study similarly revealed that CH had statistically significant association with mother's hypothyroidism [16]. Manglik *et al*. found statistically significant association of CH with mother's hypothyroidism. According to authors CH was more prevalent in newborns born to hypothyroid mothers who did not take the anti-thyroid drug during pregnancy [10]. Similar observations were also made by Ward *et al*. in USA [17] and Abbas *et al*. [18] and Karam *et al*. [19] in Pakistan.

Conclusion

The study does not support our contention that occurrence of primary congenital hypothyroidism in

Himachal Pradesh is higher than other states as incidence among 500 neonates is nil as other studies especially from South India have reported much higher incidence. However a bigger sample size would be required to say this with certainty as the national average is 1per 1172 births. The normative values of TSH at birth in our study were also comparable and neonates with TSH > 75th centile required retesting. TSH values were found to be significantly higher among babies delivered to hypothyroid mother, babies born via LSCS and large for gestational age babies.

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