

Original Research Article

Umbilical cord blood TSH level: correlation with congenital hypothyroidism

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ABSTRACT

Background: Congenital hypothyroidism is the most common preventable cause of mental retardation. Screening methods include measuring cord blood and venous blood TSH level. The objective of this study was to determine the impact if any of various risk factors affecting these levels.

Methods: It was a cross sectional study done at our hospital and 263 cord blood samples were collected and TSH levels measured. The variables included in the study are parity of mother, GDM, mode of delivery, birth weight, gestational age, sex, weight appropriate for gestation, Apgar score.

Results: In our study 35 among 263 cord blood samples were found to have CB TSH levels above the cut off value of 20 mIU/l and repeat venous sampling done on fifth day of life showed only one sample had high TSH with low free T4 levels and remaining 34 samples showed TSH levels which were significantly down from the earlier peak. The p value, ROC curve, test of significance and criterion cut off levels were made for each of the variables mentioned above. Among the variables studied, mode of delivery (<0.001), gestational age ($p=0.001$), low Apgar score ($p=0.001$) had p values which were statistically significant.

Conclusions: Incidence of congenital hypothyroidism in our study is 0.0038%. There was no sexual predilection and the high cord blood TSH levels may be due to perinatal stress factors such as emergency LSCS, low Apgar score and prematurity which had significant positive correlation as evidenced with p values (≤ 0.001).

Keywords: Thyroid stimulating hormone, Cord blood TSH, Congenital hypothyroidism, Emergency LSCS, Gestational diabetes mellitus

INTRODUCTION

Congenital hypothyroidism is the most common preventable cause of mental retardation and CH also satisfies all the criteria for being included in the newborn screening.^{1,2} It has a worldwide annual incidence of 1:4000 live birth.^{3,4} However the prevalence is much higher in several other countries including 1:748 (Iran), 1:1600 Pakistan.^{5,6} In India prevalence of CH is different in different states 1:3400 (Chandigarh) and 1:1700

(Lucknow) and 1:1700 in Hyderabad.⁷ The incidence of congenital hypothyroidism is higher in Hispanic and Asian individuals and lower in black individuals.⁸ In the majority of patients, CH is caused by an abnormal development of thyroid gland (thyroid dysgenesis) which is usually a sporadic disorder and accounts for 85% of cases. It presents in three major forms thyroid ectopy, athyreosis and thyroid hypoplasia. Thyroid ectopy accounts for two thirds of cases of thyroid dysgenesis and twice more common in female.⁹

These thyroid hormones are essential for normal growth, development and various metabolic regulations in the body. The thyroid hormone deficiency results in short stature, cretinism, intellectual disability etc. The clinical features of CH are often subtle and many newborn infants remain undiagnosed at birth.¹⁰ This is due to passage of maternal thyroid hormones across the placenta providing a protective effect, especially to the fetal brain and masking the clinical signs.¹¹ Hence universal new born screening is now the standard in most countries, as early thyroid hormone replacement in new borns with congenital hypothyroidism can prevent or minimise potentially severe developmental abnormalities associated with the illness¹² In India NBS for CH was first introduced at Waidia Hospital, Mumbai in 1982 using cordblood TSH and subsequently in 1984 using postnatal venous blood T4 levels as a pilot programme.¹³ Clinical diagnosis is difficult at birth and the time of initiation of therapy is critical in the determinant of outcome. Therefore, diagnosis and initiation of thyroxine supplements as early as possible after birth, preferably within the first two weeks of life is imperative to prevent neurocognitive impairment. Keeping in mind the devastating and irreversible adverse neurodevelopmental outcome of a delayed or missed diagnosis of CH in children, it is essential to screen for congenital hypothyroidism.

Neonatal screening methods measure either cord blood TSH level or heel prick sample at 3 to 5 days of life. Cord blood TSH is an accepted screening tool for congenital hypothyroidism. Cord blood TSH has high sensitivity but with a high false positive value and a wide range of values causes high recall rates requiring evaluation for confounding factors contributing to increase in TSH values. Moreover, various maternal and perinatal factors are known to affect TSH levels.

Objective

The objective of this study was to determine the effect of perinatal risk factors on CBTSH levels.

METHODS

This study design was a descriptive cross-sectional study which was performed in department of paediatrics, Chalmeda Anand Rao institute of Medical sciences, Karimnagar during the period of December 2017 to October 2019. In our study 263 new born cord blood samples were collected and analysed. Blood samples were drawn from umbilical cord immediately after the cord is being cut and about 2 ml of blood is collected. The sample thus collected and immediately transported to the laboratory and then analysed with electro-chemiluminescence assay.

The data of each child was collected in the specific proforma which includes the new born name, gestational age, sex, birth weight, requirement of resuscitation, Apgar score, weight, appropriate for gestation, parity of mother,

gestational diabetes mellitus and mode of delivery. Cord blood TSH levels were measured using electro-chemiluminescence immunoassay.

All neonates who had TSH level above the cut off values above 20 mu/l are for repeat TSH levels and free T4 levels in venous sample on fifth day of life. Increased TSH and decreased free T4 levels on the day 5 sample was suggestive of congenital hypothyroidism. The mean TSH levels are calculated and effect of perinatal factors on cord blood TSH levels were analysed statistically.

Inclusion criteria for the study participants were all the babies born in our hospital from January 2018 to November 2019 irrespective of gestational age, birth weight and Hemodynamically stable babies. Exclusion criteria were babies whose parents did not give consent to participate in the study and babies with congenital malformations.

Statistical tool

Data was analysed using SPSS (Statistical package for social sciences) programme version 22 for windows and for all the analysis a p value<0.05 was considered statistically significant.

RESULTS

263 new born babies irrespective of birth weight and gestational age were tested for cord blood TSH levels in the Chalmeda Anand Rao Institute of Medical Sciences over a period of 2 years (Table 1). 2 ml of umbilical cord blood was collected and was tested for TSH levels by electro-chemiluminescence method out of 263 babies tested for cord blood TSH, 34 babies had TSH>20 mu/l (cut of value in our study 57). Those babies with cord blood TSH more than 20 mIU/ml were tested again on day 5 for TSH and free T4 level, out of 34 babies tested on day 5, one baby had an increased TSH and decreased free T4 and confirmed to be a case of congenital hypothyroidism. Incidence of congenital hypothyroidism in our study was 0.0038% babies. On evaluating the variable (Table 2), gestational age with cord blood TSH among 263 samples, the mean among term babies in 224 sample was found to be 7.965 and for preterm babies it was 11.964 out of 39 sample. The p value was derived which was found to be 0.001 which was statistically significant.

On evaluating the variable mode of delivery with cord blood TSH among 263 samples, the mean among babies born by elective LSCS in 199 sample was found to be 6.543, for emergency LSCS in 42 samples were 18.2, and for NVD it was 8.382 out of 22 samples. The p value for the variable EMLSCS was found to be <0.001 which is statistically significant. Other variables such as parity of mother, gestational diabetes mellitus, gestational hypertension, birth weight, gestational age of the baby, sex of baby, weight appropriate for gestational did not affect cord blood TSH level which were statistically insignificant.

Table 1: Frequency of given parameters.

Variables		Frequency	Percentage (%)
Gestation	Primi	141	53.6
	Multi	122	46.4
	Total	263	100
	SGA	36	13.7
Appropriate for age	LGA	14	5.3
	AGA	213	81
	Total	263	100
	LSCS	199	75.7
Mode of delivery	EMLSCS	42	16
	NVD	22	8.4
	Total	263	100
	2.5 and above	145	55.1
Birth weight (kg)	<2.5	118	44.9
	Total	263	100
	Male	154	58.6
	Female	109	41.4
Gender	Total	263	100

Table 2: Factor effecting cord blood TSH.

Factors		N	Mean	SD	P value
Mode of delivery	LSCS	199	6.543	5.0927	<0.001
	EMLSCS	42	18.2	8.3808	
	NVD	22	8.382	6.0322	
Apgar score	≤7	65	13.598	9.26	0.001
	>7	198	6.904	5.43	
Gender	Males	154	8.853	7.3651	0.43
	Females	109	8.142	6.9126	
Appropriate for age	SGA	36	10.206	8.8667	0.307
	LGA	14	7.529	6.323	
	AGA	213	8.34	6.9019	
Gestational age	Term	224	7.9	6.5	0.001
	Pre-term	39	11.96	9.2	

DISCUSSION

Congenital hypothyroidism, being one of the most preventable and easily treatable causes of mental retardation, makes it a suitable candidate for universal newborn screening.

In India, 70-80% mothers are discharged within 48 hours after delivery and the major reason for missed screening is early post-natal discharge. In the developed countries, newborn screening is primarily carried out by health workers who collect dried blood spot at home, however this is difficult in our country where the population is large and the health system is overburdened as it is post-discharge sampling relies on parents to bring back to the hospital a ‘healthy normal’ newborn baby for a ‘blood’ test. Clinical diagnosis is difficult at birth and the time of initiation of therapy is critical in the determination of outcome. The ideal sample for newborn thyroid screening is still controversial. While there are several advantages as well

as disadvantages of using cord blood versus postnatal sample for screening, our experience has shown that by using cord blood TSH as a screening tool we decrease the missing rate of detection of cases of congenital hypothyroidism. Another advantage with CB TSH screening is the possibility for earlier recall, confirmation by a repeat venous sampling and treatment initiation compared to fifth day postnatal sampling. Given the devastating consequences of missed or delayed initiation of treatment in congenital hypothyroidism, this ‘high’ recall rate is still cost-effective.

Overall CB TSH trend

The main factors affecting CB TSH level are iodine status, low Apgar, emergency LSCS and preterm births. Universal iodization of salt as part of the National iodine deficiency control program was launched in India in 1992. Although the vast majority of our population uses iodised

salt, we do not have any data from our institution on the iodine status of the mothers.

There are many perinatal factors during the delivery that affect the TSH levels but we could not include all the risk factors. One of the factors that affects the CB TSH level is prematurity. The mean CBTSH levels in preterm babies was 11.967 mIU/l as compared to 7.965 mIU/l in term babies pre-term babies are more prone to stress during delivery and had high TSH value. In fact, both false positive and false negative screen TSH levels are well documented in high risk neonates such as preterm, low birth weight babies.

In our study done at CAIMS emergency LSCS, low Apgar score and pre-maturity were the variables that had significant statistical relationship (with p value ≤ 0.001) with cord blood TSH. The exact reason for this condition has not been found yet; but possibly can be explained by stress events during antepartum and intrapartum period. The other perinatal variables such as gestational age, parity of mother, sex of the new born, gestational diabetes mellitus, weight appropriate for gestation does not have significant TSH elevations and their p values remains insignificant.

Another factor that could be attributed is the increased numbers of instrumental deliveries in our population as this is a tertiary care hospital which in itself was an independent risk factor for increased in the mean CBTSH as per our study ($p < 0.01$). This was also reported by another recent Indian study where the mode of delivery and perinatal stress factors were shown to have significant impact on CBTSH levels. Therefore, we were able to explain to the parent's importance of repeat sampling for confirmation of diagnosis. In the current scenario, with CBTSH of 20 mIU/l being used as the standard cut-off value.

Among the perinatal factors which affect CBTSH level, mode of delivery was one of the important factors. In our cohort, a significant correlation was seen between CBTSH and mode of delivery ($p < 0.001$). The increase in the CB TSH particularly in instrumental deliveries may be explained by the increased perinatal stress that the new born undergoes during a difficult delivery as compared to a normal delivery/elective caesarean section. There is no consensus on what is the ideal CBTSH for new born screening for CH. The decision to increase or decrease the cut off should be made after consideration of many factors such as sensitivity, specificity, acceptable re-call rate for that population etc. The gold standard for diagnosing congenital hypothyroidism is by demonstrating elevated TSH level and low free T4 level in the confirmatory sampling. However, in our screening programme, only those with CBTSH > 20 mIU/l during the study period had a confirmatory sample of repeat TSH on day five along with free T4 done and CH ruled out or confirmed. One of the biggest problems with analyzing the sensitivity and specificity of the range of CBTSH levels was verification bias well documented with such screening tests.

As per the CES data of 2009, the overall number of institutional deliveries (rural+urban) have increased from 38.7% to 72.9%. With this increase in the percentage of institutional deliveries. The variables such as emergency LSCS and low APGAR scores were having direct correlation with the elevation of TSH levels in cord blood. Then we took venous sample for new born with TSH value more than 20mIU/l (cut off values from ROC curve) at fifth day of life. Then paired t-test done for the initial and venous blood TSH values and finding out the statistical significance. It was found to be low and this falsely elevated TSH levels was due to perinatal stress factors which also supported by other previous studies done in different centres.

There are some studies which have been performed in this same field, in which some are supporting and some results are controversial. A study by Herbstman performed in 300 new borns revealed that several factors such as maternal age, gestational diabetes mellitus, mode of delivery and pregnancy induced hypertension can affect thyroid hormone status but in/our study only mode of delivery had its effect on thyroid status in the new born baby with significant p value, maternal age, gestational diabetes mellitus did not have any significant effect.¹⁴ A study by Kim et al states that, study of perinatal factors affecting cord blood TSH levels performed in 130 neonates in Korea revealed that perinatal stress events significantly affect cord blood TSH levels which was in accordance with our study Kim et al.¹⁵ A study by Gupta et al, study revealed that there was no significant difference in cord blood TSH between male and female babies which is consistent with our study.¹⁶ Various studies are using different cut-offs for CBTSH levels ranging from 20-90 mIU/l. We have used the cut-off value for cord blood TSH level as per ROC curve is 20 mIU/l. A study by Devi et al, has taken the following range for comparison-CB TSH value < 10 mIU/l as normal, 10-20 mIU/l as borderline and > 20 mIU/ml as abnormal.¹⁷ Kaur et al, from Chandigarh has taken 9 mIU/l as the TSH cut off value.¹⁸ Mikelsaar et al from Estonia has taken CBTSH cut off value of 12 mIU/l which is lower cut off value when compared to our study.¹⁹ In our study 34 cord samples among 263 samples are found to have CB TSH levels above the cut off value of 20 and repeat venous sampling done on fifth day of life. Only one venous samples TSH levels found to be lower than cut off TSH levels. This reveals that the high cord blood TSH levels are due to perinatal stress factors such as emergency LSCS, gestational age and low Apgar score which has significant positive correlation as evidenced with p values in our study.

Limitations

To have more conclusive evidence of our findings, we have to evaluate larger number of newborns and we have to include other maternal and perinatal factors in the analysis.

CONCLUSION

Incidence of congenital hypothyroidism in our study is 0.0038% and there is no sexual predilection in our study. Our study revealed that the high cord blood TSH levels are due to perinatal stress factors such as emergency LSCS, low Apgar score and prematurity which has significant positive correlation as evidenced with p values ≤ 0.001 . In our study other variables such as parity of mother, gestational diabetes mellitus, gestational hypertension, birth weight, gestational age of the baby, sex of baby, weight appropriate for gestational age did not affect cord blood TSH level.

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