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Unfolding the perinatal factors that affect cord blood thyroid stimulating hormone levels- an experience from a rural centre in southern India

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Abstract

Objective: To evaluate the incidence of congenital hypothyroidism using cord blood thyroid stimulating hormone (CB-TSH) levels and examining the influence of maternal and perinatal factors on these levels in our cohort of babies.

Design: A cross-sectional study.

Setting: Tertiary care teaching hospital, China Kakani, A.P.

Methods: CB-TSH levels were measured in 2012 live-born neonates using electro chemiluminescence immunoassay. The effect of various maternal and perinatal factors on CB-TSH levels was analyzed statistically by multivariate analysis.

Results: The mean CB-TSH was 8.86 micro IU/ml (ranged between 0.23 to 100micro IU/ml). The incidence of high CB-TSH (>20microIU/ml) was 4.82%. CB-TSH levels were significantly raised in neonates delivered in 1st and 2nd birth order, assisted vaginal deliveries, need for emergency section, and who were born with low APGAR scores ($p < 0.01$ and Cronbach's alpha 0.932). Maternal hypothyroidism or maternal hypertension, weight appropriateness for gestation, birth weight and gestational age had no significance.

Conclusion: Upon multivariate analysis, the need for resuscitation, mode of delivery, and birth order were found to be significant factors affecting CB-TSH levels. Hence, these factors must be considered cautiously while interpreting CB-TSH values.

Keywords: Cord blood, newborn screening, perinatal factors, thyroid-stimulating hormone

Introduction

Congenital hypothyroidism is due to inadequate or absent thyroid hormone production at birth or less commonly due to transient thyroid dysfunction attributable to transplacental passage of maternal drugs, blocking antibodies, iodine deficiency or excess [13, 21, 38]. It is one of the most common and easily preventable causes of mental retardation, with an estimated incidence of 1 in 2500 to 2800 live births in India [36]. The recent multi-centric study conducted by Indian Council of Medical Research comprising of more than 100,000 newborns showed a high incidence of CH-1:1172, and this was even higher, 1:727 in babies from Southern India [2, 20, 26].

In the USA, the incidence of CH has shown an increase (from approximately 1:4,100 to 1:2,350) over the past few decades, this could be from including the babies with transient hypothyroidism (TH).

Though the exact cause for increased incidence globally is not known but factors that are implicated include changes in screening methods (lower TSH cutoff), obtaining the screening specimen earlier (closer to the TSH surge after birth), geographic and ethnic variations [39], and iodine deficiency, or excess [4, 9].

The Indian council of medical research (ICMR) introduced a screening program for congenital hypothyroidism among neonates in 2007.

Neonatal screening tests measure TSH either from cord blood or heel prick at 72 hours of life [5, 8, 15, 19, 21, 26, 30-34, 37, 39]. Though CB-TSH measurement has a high sensitivity, they also are known to have high false positivity rates [7, 14].

Various maternal and perinatal factors such as maternal age, maternal comorbidities like preeclampsia, gestational diabetes, maternal hypo or hyperthyroidism, gestational age, the

gender of the baby, perinatal insults, birth order can influence CB-TSH levels [1, 4, 6, 9-10, 16-17, 22-29]. Hence our aim was to review the influence of these factors on CB -TSH levels.

Materials and methods

Study Type

This cross-sectional study was conducted at the Neonatology unit at NRI general hospital, a tertiary care teaching hospital in a rural area, Mangalagiri, Andhra Pradesh.

Study population & duration

The study includes 2012 live-born neonates, who were born between January and December 2018.

Exclusion Criteria

Neonates with antenatally detected major malformations, life-threatening conditions during the postnatal period, mothers on anti-thyroid drugs, and critically ill mothers (on ventilator support, cardiac diseases, etc.) were excluded from the study.

Data collection

Informed consent was obtained from either of the parents. Antenatal and intrapartum information was obtained from maternal medical records.

Sample collection

Blood samples were drawn into a 5ml syringe and collected in a sterile container as per the unit protocol from the maternal end of the umbilical cord, of length 15 to 20 cms, immediately after delivering the baby. The collected sample was stored at room temperature (25°C) and transported to the laboratory within 1 hour.

Sample analysis

The sample was analyzed within 3hours by electrochemiluminescence immunoassay by Cobas e 411 analyzers with a functional sensitivity of 0.005 micro IU/ml. The normal value as per the kit is 1-20 microIU/ml, which was considered as a reliable parameter for the diagnosis of CH. All the neonates who had CB-TSH values more than 20 micro IU/ml, a repeat test of serum FT4 and TSH were done after three completed days of life (>72 hours of life).

Statistical analysis

The data were entered into the excel sheet; percentages were calculated using SPSS for windows version 12. The effect of various perinatal factors on CB-TSH was first analyzed by univariate analysis (Kruskal Wallis test) to identify differences between groups (*p*-value <0.01 was deemed as significant). Multivariate analysis (path model and factor analysis) was conducted to check the internal consistency by Cronbach’s alfa (value >0.7 was highly significant).

Ethical clearance

The hospital ethics committee approved the study.

Results and observations

Out of total 2030 enrolled births in the year 2018, three neonates were excluded from the study on the basis that their mothers were on anti-thyroid medications, one neonate born to mother on mechanical ventilator during the delivery, eight neonates had significant congenital abnormalities and life-threatening conditions during their postnatal life, three neonates CB-TSH could not be processed, two neonates died due to severe perinatal asphyxia and one from neonatal sepsis. Hence, our study population included a total of 2012 subjects, who fulfilled the inclusion.

Table 1: Profile of subjects included in our study

| Variable | Total | Mean (micro iu/ml) | Median (micro IU/ml) | p Value |
|--|-------|--------------------|----------------------|---------|
| Term (≥37weeks) | 1732 | 8.89 | 7.53 | 0.20 |
| Preterm (<37 weeks) | 280 | 8.66 | 7.59 | |
| Male | 984 | 9.03 | 7.71 | 0.12 |
| Female | 1028 | 8.70 | 7.51 | |
| AGA | 1809 | 8.87 | 7.58 | 0.40 |
| LGA | 60 | 10.8 | 7.52 | |
| SGA | 143 | 7.90 | 7.75 | |
| NVD | 1046 | 8.53 | 7.47 | 0.0002 |
| AVD | 107 | 11.68 | 8.59 | |
| Elective LSCS | 485 | 8.19 | 7.53 | 0.0002 |
| Emergency LSCS | 374 | 9.81 | 7.84 | |
| NVD | 1046 | 8.53 | 7.47 | 0.002 |
| Emergency LSCS | 374 | 9.81 | 7.84 | |
| 1 st birth order | 908 | 9.29 | 7.70 | 0.003 |
| 2 nd and higher birth order | 1104 | 8.50 | 7.53 | |
| APGAR >7 | 1835 | 7.69 | 7.28 | <0.0001 |
| APGAR <7 | 177 | 20.96 | 18.30 | |
| Routine care | 1792 | 7.57 | 7.16 | <0.0001 |
| Beyond initial steps | 220 | 19.35 | 16.95 | |
| Normotensive | 1857 | 8.88 | 7.54 | 0.19 |
| Hypertensive | 155 | 8.52 | 7.83 | |
| Euthyroid | 1743 | 8.84 | 7.53 | 0.38 |
| Hypothyroid | 269 | 8.96 | 7.88 | |

The CB-TSH values ranged from 0.23 to 100micro IU/ml with a mean value of 8.86. Out of 2012 newborns, 97(4.82%) had values more than 20 micro IU/ml, 29(1.44%)

had less than 1micro IU/ml and 1886 newborns (93.74%) had values between 1 to 20 micro IU/ml. Upon univariate analysis, CB-TSH was found to be

significantly raised in newborns delivered in 1st birth order compared to higher birth order ($p=0.03$); in newborns having APGAR<7 ($p<0.0001$) and requirement of resuscitation ($p<0.0001$), mode of delivery also had a significant effect on CB-TSH level. Infants born by assisted vaginal delivery or emergency LSCS had higher CB-TSH levels compared to infants born by normal vaginal delivery ($p=0.0002$), or by elective LSCS ($p=0.0002$). And we also observed a significantly high level of CB-TSH (0.002) in babies born by emergency LSCS than were born by NVD. Factors such as gestational age of the baby, weight appropriateness, sex of the baby, maternal hypothyroidism, or maternal hypertension did not appear to have any statistically significant influence on CB-TSH levels(table).

A multivariate analysis was conducted to assess the influence of the inter linking factors on these results. The model divided all the variables into five factors. The combined effect of all the factors was analyzed by this model.

The effect of the individual factor was further analyzed and the internal consistency was checked by Cronbach alfa for every factor (value of 0.7 is considered significant).

The variables included in the factors_ the need for emergency section, APGAR scores, a requirement of resuscitation at birth, neonates born in 1st and 2nd birth order, had a Cronbach alfa value of 0.932, showing that these factors have a very significant effect on CB-TSH levels. The variable influences were further studied for factor 1.

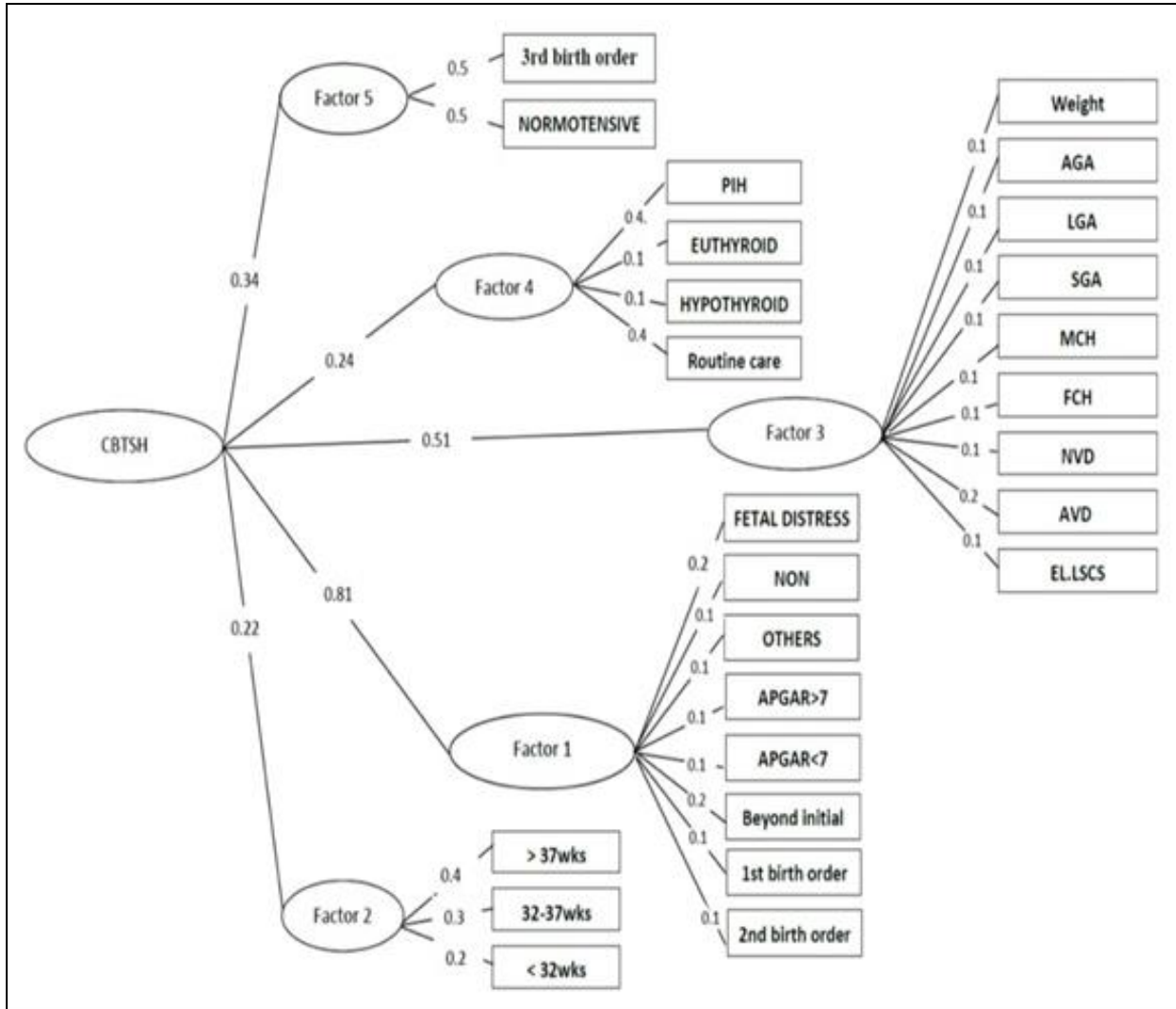


Fig 1: Path model of analysis

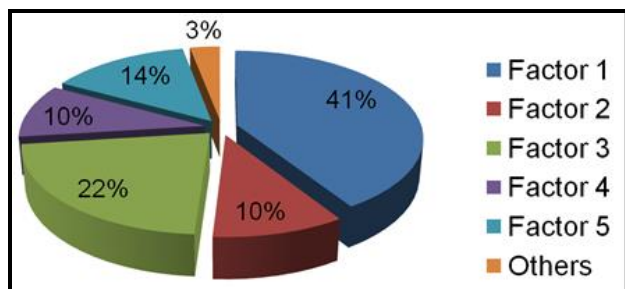


Fig 2: Showed Factor analysis

Table 2: Internal Consistency

| Factor | Cronbach's Alfa |
|--------|-----------------|
| 1 | 0.932 |
| 2 | 0.432 |
| 3 | 0.382 |
| 4 | 0.492 |
| 5 | 0.503 |

For all the babies (4.82%) who had elevated CB-TSH levels, we repeated serum TSH and free T4 after 72 hours of life for confirmation, of which one baby had an abnormal level. Hence, we initiated the therapy with levothyroxine.

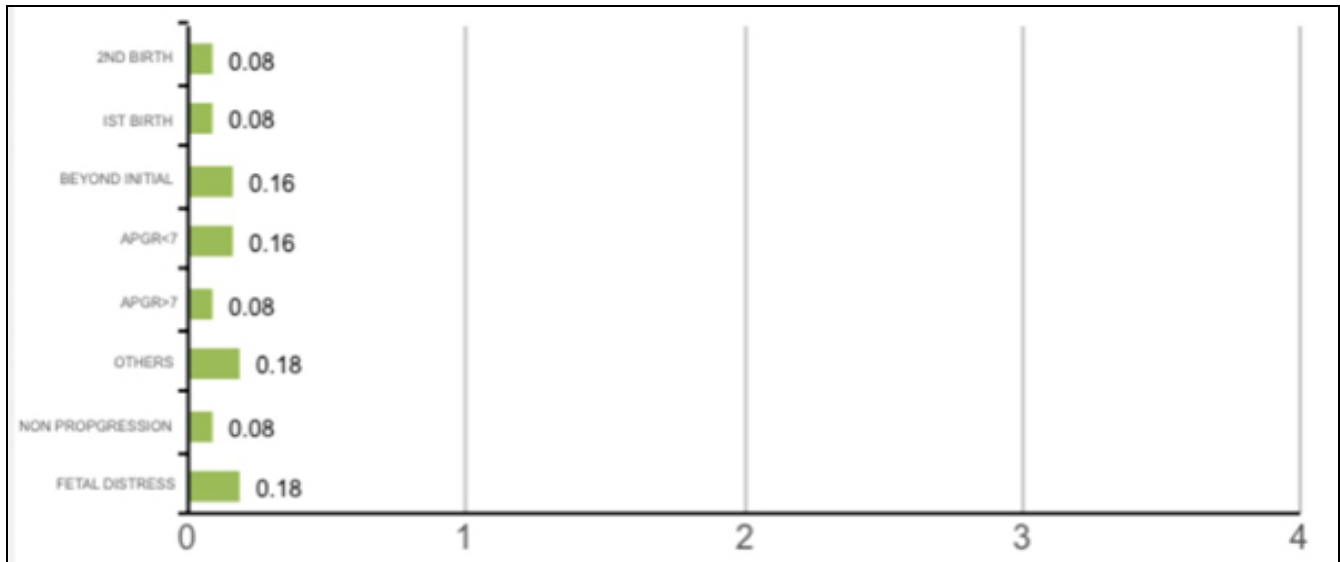


Fig 3: Variable influences

Discussion

In a global scenario, screening for congenital hypothyroidism decreases the burden of mental retardation in the society, but the screening tests are not uniform worldwide [21].

Across the world, each country or region has their own protocols for screening CH. Technically, using both T4 and TSH is superior but the cost of screening is high. In our institute we follow early discharge protocol, hence we prefer CB-TSH as screening for CH. Researchers have studied different CB-TSH cutoff values that vary between 20-90 micro IU/ml [5, 11, 12, 14, 34, 36] for recall to make the cost of rescreening low. In the Indian setting, the CB-TSH value of more than 20 micro IU/ml is considered as a safe cutoff for recall [2, 3, 5, 17-20, 31].

In our study, 4.82% of neonates had CB-TSH values more than 20 micro IU/ml, similar to Laxmi Narayana (5.42) [22] which reflects a higher recall rate when compared to Manglik (1.83%) [3] and Wu (2.27%) [37] but even higher values were observed in other studies by Nasheda (5.8%) [39], Poornima Kumar (8.1%) [29] and Gupta (11.5%) [6], etc.

Several authors have postulated that CB-TSH levels can be influenced by factors such as perinatal asphyxia, difficult deliveries_ Rashmi [9] and Laxmi Narayana [22], perinatal stress events, birth weight, gestational age,_ Tim *et al.* [27], male sex_ Chan Ly [25] and Mahin Hashemipour [28] and following instrumental delivery, or by cesarean section as the mode of delivery_ Chan Ly [25], but the mechanism is poorly understood.

The postnatal surge in TSH levels, common to all the neonates, is considered to be mediated through the alpha-adrenergic stimulation following the stress of parturition, which is likely to be more in neonates born by normal vaginal delivery than in those born by elective cesarean section for any indication. Other studies, too, demonstrated that fetal distress or failed instrumentation as an indication for LSCS were associated with higher TSH levels, representing fetal stress response to intrauterine hypoxia and acidosis during labor.

The results of various studies on the influence of perinatal factors on Cord blood TSH were paradoxical and with different results.

In our study, we observed a higher CB-TSH levels with a

significant P-value in neonates who were born with low APGAR scores, requiring resuscitation beyond routine care, those who were born by assisted vaginal delivery, emergency cesarean section for various indications, and neonates born by 1st birth order. Similar findings were observed by several authors like Gupta [6], Seth [9], Armaneni [10], and Gurudath Joshi I, Louis y Chan [25], etc. Gender had varying effect on CB-TSH level, significant in a few studies by Gupta [6], Chan y [25] while insignificant in other studies by Sunil raj [23], Laxmi Narayana [22], Fuse [4] and Seth. A [9]. However, gender had no significant effect on the mean CB-TSH level in our study.

Unlike studies that observed a negative correlation of serum TSH with gestational age_ Gupta [6], armanienI [10], Chan [26], Poornima Kumar [29], we did not find it to be significant in our study. This might be due to the practice of routinely administering antenatal steroids to women at risk of premature delivery in our labor unit. Studies show that Dexamethasone [32, 35] blunts the release of endogenous catecholamines, that might affect CB-TSH levels.

CH was confirmed in one neonate with an incidence of 1:2012 in our study, but several studies in India have reported varying rates of prevalence.

Limitations

We have presented the data derived from a single center. For more conclusive evidence, a large multi centered national trial using uniform kits and uniform cut offs for analysis is needed.

Conclusion

Perinatal stress factors, mode of delivery and birth order significantly impact CB-TSH levels. Larger trials evaluating TSH cut off values need to be conducted. Having reliable measurement techniques and standardized values will help in not only saving the cost for having to repeat a test but also allay parental anxiety.

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Conflict of interest

None

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