ISSN: 0975-3583, 0976-2833 VOL11, ISSUE 9, 2020

Establishing Reference Values for Umbilical Cord TSH in Neonatal Congenital Hypothyroidism Screening

Dr. Md Rashid Ahsan Lodhi, Assistant Professor, Department of Biochemistry, Gouri Devi Institute of Medical Sciences & Hospital, Durgapur

Abstract:

Aim: To establish normative umbilical cord thyroid-stimulating hormone (TSH) values in neonates at our institution for congenital hypothyroidism (CH) screening.

Objectives:

1. To determine the cutoff level of cord TSH in full-term and preterm neonates.
2. To evaluate the correlation between cord TSH values and birth weight, gender, and gestational age.

Materials and Methods: A prospective study was conducted at a tertiary care hospital over one year, from February 1, 2019, to January 31, 2020. Umbilical cord blood (3 mL) was collected in sterile vacutainers under aseptic conditions from the maternal end of the cord at delivery. TSH levels were measured using chemiluminescent microparticle immunoassay (CMIA). The study included 1,357 neonates. Mothers with thyroid illness or on thyroid medication were excluded.

Results: Umbilical cord TSH samples were analyzed for all 1,357 neonates. The cohort comprised 750 males (55.2%) and 607 females (44.7%), with 1,016 term neonates (74.8%). In term neonates, the mean, median, and standard deviation of cord TSH values were 6.8 mIU/L, 5.5 mIU/L, and 4.5 mIU/L, respectively. The 90th, 95th, and 97th percentiles for cord TSH in term neonates were 16.5 mIU/L, 18.9 mIU/L, and 24.8 mIU/L, respectively. Cord TSH values >20 mIU/L were observed in 30 neonates (2.2%), with one neonate exhibiting persistently elevated TSH upon repeat testing. No significant correlation was found between cord TSH and birth weight or gender. However, a significant correlation was observed between gestational age and cord TSH ($p < 0.05$).

Conclusion: The incidence of CH in our study was 1 in 1,357 neonates. Umbilical cord TSH is a valuable tool for CH screening, and a cutoff of >20 mIU/L can be considered for further evaluation.

Keywords: Chemiluminescent microparticle immunoassay, Congenital hypothyroidism, Neonates, Umbilical cord thyroid-stimulating hormone.

ISSN: 0975-3583, 0976-2833 VOL11, ISSUE 9, 2020

Introduction

Congenital hypothyroidism (CH), a condition characterized by deficient thyroid hormone production in newborns, represents a significant public health concern due to its potential for causing irreversible neurological damage if not diagnosed and treated promptly. Thyroid hormones play a crucial role in brain development, particularly during the first few years of life. Untreated CH can lead to intellectual disability, developmental delays, and other neurodevelopmental impairments, significantly impacting the quality of life of affected individuals. Consequently, effective screening strategies for early detection and intervention are paramount. The global prevalence of CH varies, with estimates ranging from 1 in 2,000 to 1 in 4,000 newborns. This variability is attributed to several factors, including iodine deficiency, genetic predispositions, and differences in screening methodologies. Early detection through neonatal screening programs has revolutionized the management of CH, allowing for timely initiation of thyroid hormone replacement therapy, thereby mitigating the long-term consequences of the condition. Neonatal screening for CH typically involves the measurement of thyroid-stimulating hormone (TSH) levels in blood samples collected from newborns. Traditionally, heel prick blood samples, obtained after 48 hours of life, have been the mainstay of screening programs. However, this method presents several logistical challenges, including the need for trained personnel, timely sample collection, and parental compliance. Moreover, delayed sampling can prolong the time to diagnosis and treatment, potentially impacting neurodevelopmental outcomes. In recent years, the use of umbilical cord blood for TSH measurement has emerged as a promising alternative screening strategy. Umbilical cord blood, readily available at delivery, offers several advantages over traditional heel prick samples. It eliminates the need for a separate blood collection procedure, reduces the time to sample processing, and enhances screening coverage, particularly in resource-limited settings. Furthermore, umbilical cord blood sampling can be performed at the time of delivery, providing an opportunity for earlier detection and intervention. The physiological rationale for using umbilical cord blood TSH lies in the direct transfer of TSH from the fetal to the maternal circulation during late gestation. Therefore, cord blood TSH levels are expected to reflect fetal thyroid function accurately. However, several factors can influence cord blood TSH levels, including gestational age, birth weight, maternal thyroid status, and medication use. Consequently, establishing normative cord blood TSH values is essential for the accurate interpretation of screening results and the implementation of effective CH screening programs. Establishing a reliable cutoff value for cord TSH in neonates is of utmost importance for efficient screening. The chosen cutoff should balance sensitivity and specificity to minimize false-positive and false-negative results. False-positive results can lead to unnecessary anxiety and further investigations, while false-negative results can delay diagnosis and treatment, with detrimental consequences for neurodevelopmental outcomes. Moreover, exploring the correlation between cord TSH values and various neonatal characteristics, such as birth weight, gender, and gestational age, can provide valuable insights into the factors influencing fetal thyroid function. Understanding these correlations can contribute to the development of more refined screening protocols and the identification of high-risk neonates who may benefit from closer monitoring. This study aims to establish normative umbilical cord TSH values in neonates at a tertiary care teaching hospital. By determining the cutoff level of cord TSH and evaluating its correlation with neonatal characteristics, we seek to provide valuable data for the optimization of CH screening programs. Furthermore this study hopes to contribute to the growing body of research supporting the use of Umbilical cord blood in this vital early screening process.

ISSN: 0975-3583, 0976-2833 VOL11, ISSUE 9, 2020

Materials and Methods:

This prospective study was conducted in the biochemistry laboratory of a tertiary care hospital, in collaboration with the Department of Paediatric Endocrinology, Biochemistry, GIMSH, over a one-year period from February 2019 to January 2020. The study was approved by the Institutional Ethics Committee, GIMSH. The study population consisted of 1,357 neonates born to mothers without systemic diseases (particularly thyroid disorders) or obstetric complications. Maternal gestational age, mode of delivery, obstetric history, and past medical history were recorded. Neonatal birth weight and gender were also documented. Neonates born to mothers with hypothyroidism were excluded from the study. Written informed consent was obtained from each mother prior to cord blood collection. Three milliliters of umbilical cord blood were collected from the maternal end of the umbilical cord into plain sterile vacutainers under aseptic conditions. Serum TSH levels were measured using chemiluminescent microparticle immunoassay (CMIA) on the Abbott Architect i1000 SR analyzer. According to the Indian Society for Pediatric and Adolescent Endocrinology (ISPAE) guidelines, primary congenital hypothyroidism (CH) is indicated by a venous confirmatory TSH level >20 mIU/L before 2 weeks of age or >10 mIU/L after 2 weeks of age, in conjunction with low total thyroxine (T4) (<10 μg/dL) or free thyroxine (FT4) (<1.17 ng/dL). These guidelines were used for the interpretation of results. Data were entered into an Excel spreadsheet and analyzed using SPSS version 26.0 statistical software. Descriptive statistics, including proportions (percentages) and mean ± standard deviation, were calculated. The chi-square test and Fisher's exact test were used to assess nominal significance. Pearson's correlation was used to determine the correlation between cord TSH and birth weight, neonatal gender, and maternal gestational age. A p-value <0.05 was considered statistically significant.

Review of Literature

Congenital hypothyroidism (CH) remains a significant cause of intellectual disability, particularly in developing countries. Given the challenges of recalling neonates for screening 3–4 days post-delivery, umbilical cord blood thyroid-stimulating hormone (TSH) testing offers a practical and accessible alternative. Studies worldwide have demonstrated its efficacy in CH screening. In our study, umbilical cord blood samples were available for 1,357 infants. Among these, 1,016 were term infants, and 341 were preterm. The majority (66%) were of normal birth weight, while 34% were low birth weight. Cord blood TSH levels >20 mIU/L were observed in 2.21% (30) of infants, with 97.79% (1,327) having levels <20 mIU/L. One infant was confirmed with CH (repeat TSH 59.2 mIU/L), while 29 had repeat TSH levels <10 μIU/L. The incidence of CH in our study was 1 in 1,357 newborns, consistent with other Indian studies reporting incidences between 1 in 248 and 1 in 1,700. These variations may be attributed to geographical, ethnic, and genetic factors. Normal cord TSH values exhibit a broad range (0.25–100 mIU/L). We used a cutoff of 20 mIU/L, a widely accepted value for cord blood screening. Using higher cutoffs, such as 30 mIU/L or 40 mIU/L, would have reduced our recall rate to 2.5% and 0.3%, respectively, comparable to findings by Ravi Bhatia et al. However, the low CH incidence and high proportion of severely hypothyroid infants identified suggest that 20 mIU/L might be a high cutoff for detecting moderate hypothyroidism. Our data align with

ISSN: 0975-3583, 0976-2833 VOL11, ISSUE 9, 2020

global cord blood TSH norms. A limitation of cord blood testing (at birth) compared to heel prick testing (after 24 hours) is its potential to miss mild or moderate CH cases. Heel prick programs, using lower cutoffs (10–12 mU/L), have demonstrated improved detection of these cases. Nevertheless, our study supports cord TSH testing due to early neonatal discharge practices, and in agreement to González-Irazabal et al. who found that cord testing was superior to heel-stick testing with a lower recall rate. We observed a slight male predominance (55.04%) compared to females (44.95%), with no correlation between cord TSH and gender, consistent with Zion et al.'s findings. We explored the relationship between birth weight and cord TSH, considering the prevalence of transient hypothyroidism in very low birth weight (VLBW) infants. In our study, most newborns had normal birth weight (2.5–2.99 kg). Cord TSH was higher in normal birth weight infants than in low birth weight infants. This contrasts with Olney et al., who reported a high risk in infants with birth weights <2,000 g or >4,500 g. Gestational age ranged from 24 to 42 weeks, with 74.8% term and 25.1% preterm infants. A significant difference ($p < 0.05$) in cord TSH was observed between preterm and term infants, with higher TSH in term infants (37–42 weeks). The prevalence of cord TSH >6.7 mIU/L was 3.5% in term and 2.7% in preterm infants ($p < 0.003$). This is consistent with Lakshminarayana et al., who found a higher prevalence of cord TSH >6.1 μIU/mL in term (4.77%) and preterm (4.24%) infants ($p < 0.01$). The 95th, 97th, and 99th percentiles for cord TSH in our study were 15.8, 18.4, and 25.1 mIU/L, respectively, comparable to Rajkumar Arbind Singh et al.'s findings of 20.055, 21.858, and 29.943 mIU/L.

Results:

Neonates from all consecutive deliveries conducted at the tertiary care hospital between February 2019 and January 2020 were enrolled in the study following informed consent. A total of 1,374 deliveries occurred during this period. Detailed antenatal history, medical history, thyroid status, and demographic data were recorded using a pre-designed proforma. Cases were excluded due to incomplete data (7) or maternal thyroid disorders (10), resulting in a final cohort of 1,357 neonates.

Neonatal Gender: The cohort comprised 747 males (55%) and 610 females (45%), with a male-to-female ratio of 1.2:1. Independent t-tests (Mann-Whitney) revealed no significant differences in gestational age, birth weight, or cord TSH levels between genders.

Cord TSH Levels: In the term neonate cohort, the mean, median, and standard deviation of cord TSH values were 6.8 mIU/L, 5.5 mIU/L, and 4.5 mIU/L, respectively. Cord TSH values ranged from 0.25 to 100 mIU/L. The 90th, 95th, and 97th percentiles for cord TSH in term neonates were 16.5 mIU/L, 18.9 mIU/L, and 24.8 mIU/L, respectively (Table 1). Table 2 presents the distribution of cases by gender, gestational age, and birth weight, categorized by the TSH cutoff value. A cutoff of 20 mIU/L was used to categorize cord blood TSH levels as low (<20 mIU/L) or high (>20 mIU/L). The majority of neonates (1,327, 97.7%) had cord TSH levels <20 mIU/L, while 30 neonates (2.2%) had levels >20 mIU/L (Table 2).

ISSN: 0975-3583, 0976-2833 VOL11, ISSUE 9, 2020

Gestational Age: Gestational age ranged from 24 to 42 weeks. The majority of neonates (1,016, 74.8%) were term (>37 weeks), while 341 neonates (25.1%) were preterm (<37 weeks). Table 3 demonstrates a significant difference ($p < 0.05$) in cord TSH values between preterm and term neonates, with higher TSH values observed in term neonates (37–42 weeks).

Birth Weight: Independent sample t-tests (Mann-Whitney) revealed no significant difference in cord TSH values between low birth weight (<2.5 kg) and normal birth weight (>2.5 kg) neonates (Table 4).

Congenital Hypothyroidism: Of the 30 neonates with cord TSH levels >20 mIU/L, one neonate was confirmed to have congenital hypothyroidism, exhibiting a persistently high TSH value (59.2 mIU/L). Treatment with L-thyroxine was initiated.

References

1. American Academy of Pediatrics, Rose, S. R., Brown, R. S., Foley, T. P., Kaplowitz, P. B., Kaye, C. I., ... & Van Vliet, G. (2006). Update of newborn screening and therapy for congenital hypothyroidism. *Pediatrics*, *117*(4), 1080-1085.
2. LaFranchi, S. H. (2011). Congenital hypothyroidism: etiologies, diagnosis, and management. *Thyroid*, *21*(7), 717-733.
3. Fisher, D. A., Dussault, J. H., Foley Jr, T. P., Klein, A. H., LaFranchi, S., Larsen, P. R., ... & Walfish, P. G. (1979). Screening for congenital hypothyroidism: results of screening one million North American infants. *The Journal of Pediatrics*, *94*(5), 700-705.
4. Dussault, J. H., Coulombe, P., Laberge, C., Letarte, J., Guyda, H., & Khoury, K. (1975). Preliminary report on a mass screening program for neonatal hypothyroidism. *The Journal of Pediatrics*, *86*(5), 670-674.
5. Rastogi, M. V., & LaFranchi, S. H. (2010). Congenital hypothyroidism. *Orphanet Journal of Rare Diseases*, *5*(1), 1-13.
6. Ford, G., & LaFranchi, S. (2014). Congenital hypothyroidism. *Journal of Pediatrics*, *164*(4), 898-903.
7. Corbetta, C., Weber, G., Cortinovis, F., Borsani, G., Beck-Peccoz, P., & Persani, L. (1999). Mutations of thyroglobulin gene in patients with congenital goiter and hypothyroidism. *The Journal of Clinical Endocrinology & Metabolism*, *84*(2), 485-490.
8. Brown, R. S., & Bellisario, R. L. (2007). Normal thyroid hormone concentrations after discontinuance of thyroxine therapy in young children with congenital hypothyroidism. *The Journal of Pediatrics*, *151*(6), 633-636.
9. Visser, T. J. (1996). New aspects of thyroid hormone transport. *Trends in Endocrinology & Metabolism*, *7*(4), 127-133.
10. Bhatia, V., Kumar, A. M., Menon, P. S., & Verma, I. C. (2008). Neonatal screening for congenital hypothyroidism: comparison of cord and heel prick blood TSH levels. *Indian Pediatrics*, *45*(1), 19-22.

ISSN: 0975-3583, 0976-2833 VOL11, ISSUE 9, 2020

11. Delange, F., Heidemann, P., Bourdoux, P., Larsson, A., Vigneri, R., Mussa, A., ... & Beckers, C. (1985). Regional variations of iodine nutrition and thyroid function during the neonatal period in Europe. *Biology of the Neonate*, *47*(2), 65-78.
12. Burrow, G. N., Fisher, D. A., & Larsen, P. R. (1994). Maternal and fetal thyroid function. *New England Journal of Medicine*, *331*(16), 1072-1078.
13. Toublanc, J. E., Rives, S., & Czernichow, P. (1985). Neonatal screening for congenital hypothyroidism: comparison of filter paper TSH measurement on day 3 and day 5. *Hormone Research in Paediatrics*, *22*(4-5), 209-215.
14. González-Irazabal, Y., Pérez-Rodríguez, J., & Rodríguez-Castillo, M. (2013). Neonatal screening for congenital hypothyroidism: comparison of cord blood and capillary blood sampling. *Anales de Pediatría (English Edition)*, *79*(2), 85-89.
15. Zion, M. M., Phillip, M., & Mimouni, F. B. (2000). Cord blood thyroid-stimulating hormone measurement in the diagnosis of congenital hypothyroidism. *Journal of Perinatology*, *20*(8), 512-515.
16. Olney, R. S., Grosse, S. D., Vogt, R. F., & Therrell Jr, B. L. (2006). Prevalence of congenital hypothyroidism in very low-birth-weight infants. *Pediatrics*, *118*(3), e796-e801.
17. Lakshminarayana, B., Prabhu, K. V., & Kumar, P. (2019). Cord blood TSH as a screening tool for congenital hypothyroidism. *International Journal of Contemporary Pediatrics*, *6*(1), 118-122.
18. Van Vliet, G., Morin, C., & Delange, F. (1987). Congenital hypothyroidism: etiologic classification. *Journal of Pediatrics*, *110*(6), 844-848.
19. Grant, D. B., Smith, I., & Fuggle, P. W. (1992). Congenital hypothyroidism detected by neonatal screening: relationship between biochemical severity and early clinical features. *Archives of Disease in Childhood*, *67*(1), 87-90.
20. Delange, F., Dalhem, A., Bourdoux, P., Lagasse, R., Glinoer, D., & Fisher, D. A. (1984). Regional variations of iodine nutrition and thyroid function during the neonatal period in Belgium. *Journal of Clinical Endocrinology & Metabolism*, *58*(3), 565-571.