

Screening for congenital hypothyroidism and the association of congenital hypothyroidism with screening thyroid-stimulating hormone levels of 10–20 mIU/L among inborn neonates in a government tertiary care hospital of North Kerala

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ABSTRACT

Background: Newborn screening for hypothyroidism is necessary because of the high incidence of congenital hypothyroidism (CH) in various studies. The necessity of doing confirmatory tests with screening thyroid-stimulating hormone (TSH) levels as low as 10 mIU/L is still unclear. **Objectives:** To find out the incidence of CH as well as its association with screening TSH levels between 10 and 20 mIU/L. **Materials and Methods:** In a prospective observational study, inborn neonates irrespective of their gestational age were enrolled and screened for CH using venous TSH levels. Those with TSH levels ≥ 10 mIU/L were subjected to confirmatory tests (free T4 and TSH levels) for the diagnosis based on the recommendations of the Indian Society for Pediatric and Adolescent Endocrinology. The various characteristics of the neonates such as birth weight, gender, gestational age, and maternal thyroid status were recorded and their relationship with subsequent CH was studied. The association between screening TSH levels 10–20 mIU/L and CH was also analyzed, and the cutoff point for screening TSH was determined using receiver operated characteristic (ROC) curve. **Results:** A total of 2407 neonates were screened for CH, out of which 357 (14.8%) were retested with free T4 and serum TSH levels. The incidence of CH was 1 in 160.5 (6.2/1000 live births). The male to female ratio was 1.5:1. There was a significant association between screening TSH levels and CH. A total of 0.6% of neonates diagnosed with CH had screening TSH levels in the range of 10–20 mIU/L, but this association was not found to be statistically significant, and the ideal cutoff value was 19.45 mIU/L based on ROC curve. **Conclusion:** The incidence of CH is high which upholds the need for universal newborn thyroid screening. Although there is no statistically significant association between CH and screening TSH levels 10–20 mIU/L, a few cases are likely to be missed on using a higher screening TSH cutoff value of 20 mIU/L.

Key words: Congenital hypothyroidism, Incidence, Newborn screening, Screening thyroid-stimulating hormone levels

Early diagnosis of congenital hypothyroidism (CH) is important because it is one of the most common preventable causes of mental retardation [1]. Most cases of CH are sporadic and occur in one in 3000–4000 infants [2]. The multicentric study screening above 1 lakh neonates born throughout India launched by Indian Council of Medical Research (ICMR) National Task Force Team on Newborn Screening at All India Institute of Medical Sciences New Delhi (2007–2012) reveals a much higher incidence of CH all over India at 1 in 1172, particularly in South Indian population (1 in 727) [3]. Hypothyroidism in newborns is often overlooked as most of them with CH have normal appearance without any physical signs. This emphasizes the need for newborn screening for hypothyroidism [4].

CH includes subclinical CH and is a generic term for congenital thyroid hormone deficiency due to a morphological

abnormality or dysfunction of the thyroid gland that develops in the fetal or perinatal stage. Subclinical CH has no symptoms, i.e., it is a subclinical disease, but some patients may have a low thyroid hormone level [5].

Most of the newborn screening programs recommend to measure thyroid-stimulating hormone (TSH) levels initially followed by T4 levels, if TSH levels are elevated. The optimal time for screening is 48–72 h of age. This is to minimize the false positive high values due to the physiological neonatal TSH surge that elevates TSH levels and causes dynamic T4 and T3 changes in the first 1 or 2 days after birth. Furthermore, for infants <1500 g birth weight, repeat specimens should be sent at 2, 6, and 10 weeks of age due to risk of delayed TSH elevation [6].

Many screening programs using TSH levels above 20–25 mIU/L recall neonates [2]. TSH levels >50 mIU/L are most likely to have permanent CH, whereas a TSH level

between 20 and 49 mIU/L is frequently a false positive or represents transient hypothyroidism [2]. In a survey of pediatric endocrinologists, infants with TSH ≥ 10 mIU/L at <6 months after birth (excluding neonates) and those with TSH ≥ 5 mIU/L at 12 months after birth were considered to have abnormalities (morphological abnormalities such as aplasia, hypoplasia, and dysmorphogenesis) to require treatment [5]. However, there are no global criteria for the range of abnormal TSH, and diagnosis depends on the discretion of the clinician [5]. Patients with slightly high TSH may subsequently be diagnosed with persistent CH [5]. Therefore, infants in such cases should be very carefully followed up from birth.

The TSH cutoff point should be set in a way as to diagnose all cases of CH. Considering the deleterious effects of CH which is preventable studies need to be done on the incidence of CH among newborns with lower TSH levels. This would also aid in having an appropriate cutoff point for early diagnosis and treatment. The aim of the study was to assess incidence of CH among newborns born in a tertiary care hospital in North Kerala and to study the association of CH with screening TSH levels 10–20 mIU/L.

MATERIALS AND METHODS

After obtaining approval from the Institutional Ethics Committee, this hospital-based prospective observational study was conducted in the newborn unit of Government Medical College, Kannur, over a period of 13 months from August 2017 to August 2018. All inborn neonates irrespective of the period of gestation were included. Babies who expire or were/referred to another hospital before 48 h of life were excluded from the study. Samples were collected using consecutive sampling design.

Venous blood was drawn from the study subjects after 48 h of life and analyzed for serum TSH levels after getting informed consent from the parents. Serum TSH level was analyzed in the certified laboratory of the hospital by chemiluminescent immunoassay. Babies with TSH levels above 10 mIU/L were retested for free T4 and TSH levels within 2 weeks and if TSH remained above 10 mIU/L babies were recalled after 21 days of age for repeat testing. The diagnosis was based on consensus guidelines of the Indian Society for Pediatric and Adolescent Endocrinology [7]. If venous TSH levels were ≥ 10 mIU/L after 3 weeks of age, treatment was started even if free T4 concentrations were normal. If free T4 levels were low (<1.1 ng/dl) irrespective of TSH or if free T4 <1.17 ng/dl with TSH >20 mIU/L (TSH >10 mIU/L for age >2 weeks), then also treatment was started immediately.

The characteristics of newborn infants such as birth weight, period of gestation, gender, maternal thyroid status, and their relation with CH were studied. The association between CH and screening TSH levels was analyzed using Fischer's exact test and Chi-square test. $p < 0.05$ was considered significant. The receiver operated characteristic (ROC) curve was used to determine the cutoff point and sensitivity of screening TSH.

RESULTS

During the current study over a period of 13 months, 2407 newborn babies were screened for CH after 48 h of life. The mean age of screening was 3.25 ± 0.74 days. There were 357 babies (14.8%) with serum TSH ≥ 10 mIU/L who were retested with serum-free T4 and TSH levels within 2 weeks. The mean TSH levels of the retested neonates were 15.76 ± 12.62 (10–100). Out of 357 of the retested neonates, 219 (61.3%) were males and 138 (38.7%) were females. The mean birth weight and mean gestational age were 2.61 ± 0.62 kg and 37.01 ± 2.43 weeks, respectively. Screening characteristics of retested neonates are presented in Table 1.

There was a significant association between screening TSH levels and CH (using Fisher's exact test, $p < 0.001$). Incidence of CH in the present study was 0.62%, i.e., 6.2 per 1000 live births (1 in 160.5). Among neonates with CH, 9 (60%) were males and 6 (40%) were females (male: female ratio 1.5:1). Of the CH cases, 10 were full term (66.7%) and 5 (33.3%) were preterm infants among which 2 (13.3%) were between 28 and 34 weeks and 3 (20%) were in the 34 and 37 weeks category. The birth weight was normal in 10 (66.7%) neonates, 2 (13.3%) had very low birth weight, and 3 (20%) had low birth weight. There was no statistical association between birth weight or gestational age and hypothyroidism. In two neonates (13.3%) with CH, mother had hypothyroidism, but there was no statistical association. The proportion of retested neonates diagnosed as CH based on screening TSH levels is given in Table 2.

The area under the curve level for screening TSH ≥ 10 mIU/L according to the confirmatory thyroid function tests, free T4 and TSH (gold standard) was 0.960 (Fig. 1). Based on ROC curve, the appropriate cutoff point for retesting for screening TSH with acceptable sensitivity and specificity was 19.455. The sensitivity and specificity for determined cutoff point (19.455) were 93.3% and 90.1%, respectively. The sensitivity and specificity of various TSH cutoff values between 10 and 20 mIU/L are given in Table 3.

Table 1: Screening characteristics of the retested neonates

Variables	Number (%)
Birth weight (g)	
≥ 2500	231 (64.7)
1500–2500	104 (29.1)
1000–1500	15 (4.2)
<1000	7 (2)
Gestational age (weeks)	
Term (≥ 37)	228 (63.9)
34–37	94 (26.3)
28–34	27 (7.6)
<28	8 (2.2)
Sex	
Male	219 (61.3)
Female	138 (38.7)
Maternal thyroid status	
Normal	324 (90.7)
Hypothyroidism	30 (8.4)
Hyperthyroidism	3 (0.8)

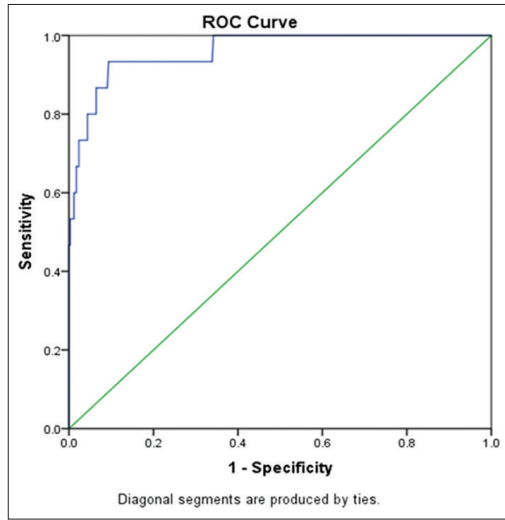


Figure 1: Area under the curve (AUC) level for screening TSH \geq 10 mIU/L

Of the 15 cases diagnosed as CH, free T4 levels were low with TSH levels >20 mIU/L in 12 cases. Normal FT4 and TSH 10–20 mIU/L were seen in 1 case and when retested after 21 days of age was confirmed to have CH (low FT4 and TSH >20 mIU/L). Two babies had normal FT4 and TSH >20 mIU/L who also on retesting after 21 days of age showed low FT4 and TSH >20 mIU/L and were put on treatment. None of the babies in the study had low free T4 levels alone (<1.1) as per consensus to diagnose CH. The thyroid hormone levels of the cases diagnosed are shown in Table 4.

DISCUSSION

The overall objective of the study was to find out the incidence of CH among babies admitted in Government Medical College, Kannur, and to know if those babies with screening TSH between 10–20 mIU/L need to be retested for diagnosing CH as against the conventional practice of retesting those with levels above 20 mIU/L.

The incidence of CH in the present study is 1 in 160.5 among inborn infants. Recent Indian studies have suggested a high incidence of CH. Desai *et al.* reported 1 in 2640 in 1997 [8]. Other studies have reported the incidence as 1 in 1700 neonates from Hyderabad, 2.1 in 1000 from Kochi, and 1 in 1042 in another study recently from Bangalore (instead of UP) [9-11]. All these data show a high prevalence which further implies better screening strategies with accessibility and probably iodine deficiency in mothers which require further studies to make an authentic statement. The variable results in the studies could be due to the variation in sample sizes and the inclusion of preterm infants in the sample in some studies.

The female to male sex ratio of CH in the study was 1:1.5, and gender was not a significant risk factor for the occurrence. This is in accordance with a study from Iran reporting a female to male ratio of 1:1.4 [12]. A recent meta-analysis found CH incidence of 1.35 (95% confidence interval: 0.99, 1.83) with significant

Table 2: Congenital hypothyroidism and screening TSH levels

Screening TSH (mIU/L)	CH (%)	No CH (%)	Total
10–20	2 (0.6)	313 (99.4)	315
≥ 20	13 (31)	29 (69)	42
Total	15	342	357

CH: Congenital hypothyroidism, TSH: Thyroid-stimulating hormone

Table 3: Sensitivity and specificity of screening TSH cutoff values

Screening TSH cutoff (mIU/L)	Sensitivity (%)	Specificity (%)
10.02	100	26
13.52	100	65.2
15.02	93.3	73.7
19.45	93.3	90.1

TSH: Thyroid-stimulating hormone

Table 4: Thyroid hormone profile in newborns with congenital hypothyroidism

Screening TSH (mIU/L)	FT4 (ng/dl) and TSH (mIU/L)	FT4 and TSH at 21 days
10–20		
19.74	1.9, 10.7	1.4, 34.4
13.6	1.18, 20.2	
>20		
26.7	1.6, 24.08	
45.3	1, 72.5	
29	1.8, 37.95	1.5, 35
22.01	1.6, 24.9	
82.6	1.5, 100	
>100	0.96, >100	
24.46	1.7, 30.2	1.4, 43.9
21.29	0.122, >100	
>100	1.19, >100	
>100	0.25, >100	
>100	0.57, >100	
>100	1.06, 96.69	
>100	1.1, >100	

TSH: Thyroid-stimulating hormone

heterogeneity among studies and a higher risk in girl gender which is in sharp contrast to our study [13]. This difference might be due to small sample size in our study.

We found no significant association between CH and other variables such as birth weight, gestational age, and maternal hypothyroidism. The study from Iran shows a similar picture [12]. Although not statistically significant, maternal hypothyroidism was present in 13.3% of neonates diagnosed with CH. This emphasizes the need for screening mothers for hypothyroidism and to conduct further studies to determine the role of genetic factors in CH.

We used the screening TSH cutoff of 10 mIU/L and 357 out of 2407 neonates (14.8%) had to be retested. The retest rate was 14.8% using a screening TSH cutoff of ≥ 10 mIU/L. Using this cutoff, 15 cases were diagnosed (4.2%) as CH and were started on treatment with levothyroxine. Of these, 315 (88.2%) had TSH 10–20 mIU/L and 42 (11.8%) had TSH ≥ 20 mIU/L. Of the 315 cases with

screening TSH 10–20 mIU/L, 2 cases (0.6%) were subsequently diagnosed to have CH, and there was no statistical association.

The screening TSH cutoff value of 10 mIU/L in the current study detected 15 cases of CH with a sensitivity of 100% and specificity of 26% based on the ROC curve. At the TSH cutoff value of 13.52, the specificity increased to 65%. The ideal cutoff in the present study was 19.45, with a sensitivity of 93.3%. Since sensitivity is more important for a screening test, it is prudent to have a high index of suspicion with close follow-up for TSH values at least above 13 mIU/L. If a higher TSH cutoff value of 20 mIU/L been used, 2 of the confirmed cases (13.3%) would have been missed. In a Brazilian study where the prevalence of CH was 1:2234, a screening TSH cutoff value of 5 mIU/L detected 50 cases of CH with a sensitivity of 100% [14]. Botler *et al.* analyzed various TSH cutoff values for detecting CH and 42 cases were found using a cutoff value of ≥ 20.0 mIU/L in 2005, but 165 cases were found in 2007 when the cutoff value was reduced to ≥ 10.0 μ IU/mL [15]. Korada *et al.* detected 120 infants with CH using a TSH cutoff value of 6.0 mIU/L [16].

In an Italian study, a screening TSH cutoff of < 15 mIU/L was used, and it was found that among those diagnosed with CH with screening TSH values below 15 mIU/L, 21.6% had permanent hypothyroidism and 54% had transient hypothyroidism [17]. In a study done in preterm infants of 21–35 weeks, a lower cutoff of 6 mIU/L was used and it was concluded that using such a lower cutoff in preterm infants, CH could be diagnosed earlier and repeat testing could be avoided at 36 weeks since they usually exhibit a delayed TSH rise [18]. A study by ICMR task force in infants of 34 weeks and above recommends that 10 mIU/L is the 97.5th percentile value even when corrected for gender, birth weight and age at sampling and thus 10 mIU/L seems to be the right cutoff beyond which a second sample should be sought [19].

This study reinforces the fact that CH is highly prevalent in our population and that a vigilant eye with meticulous screening is needed to pick up the cases. Many studies mentioned above reported the occurrence of CH in newborns with lower screening TSH levels. Considering the high incidence of CH in the area as found in the present study, accepting a sensitivity of 100% and specificity of 65% for a screening TSH cutoff value of 13.52 mIU/L seems justifiable.

The main limitation of our study was a small sample size. Larger sample size would have been needed to get a statistical association between TSH levels 10–20 mIU/L and CH. Further studies on a larger population are necessary to eliminate this gray area. Another limitation was that we did not categorize neonates into preterm and terms which might be the reason for the heterogeneity in the incidence of CH when compared to other Indian studies.

CONCLUSION

The high incidence of CH in this study corroborates the need for universal screening of newborns. The occurrence of CH in babies with screening TSH levels 10–20 mIU/L though in a smaller

proportion raises the question whether the cutoff of screening TSH should be brought down to a lower level. More studies on a larger sample are needed to hit on a solution.

REFERENCES

1. Ayyad AH, Hashemipour M, Hovsepian S, Kooshki AM, Afshari M. The relation between serum and filter paper TSH level in neonates with congenital hypothyroidism. *Adv Biomed Res* 2014;3:23.
2. Büyükgöbüz A. Newborn screening for congenital hypothyroidism. *J Clin Res Pediatr Endocrinol* 2013;5 Suppl 1:8-12.
3. Prabhu SR, Mahadevan S, Jagadeesh S, Suresh S. Congenital hypothyroidism: Recent Indian data. *Indian J Endocrinol Metab* 2015;19:436-7.
4. Büyükgöbüz A. Congenital hypothyroidism clinical aspects and late consequences. *Pediatr Endocrinol Rev* 2003;1 Suppl 2:185-90.
5. Mass Screening Committee, Japanese Society for Pediatric Endocrinology, Japanese Society for Mass Screening, Nagasaki K, Minamitani K, Anzo M, *et al.* Guidelines for mass screening of congenital hypothyroidism (2014 revision). *Clin Pediatr Endocrinol* 2015;24:107-33.
6. Eichenwald EC, Martin C, Stark AR. Cloherty and Stark's Manual of Neonatal Care. Philadelphia, PA: Wolters Kluwer; 2017.
7. Desai MP, Sharma R, Riaz I, Sudhanshu S, Parikh R, Bhatia V. Newborn screening guidelines for congenital hypothyroidism in India: Recommendations of the Indian society for pediatric and adolescent endocrinology (ISPAE)-Part I: Screening and confirmation of diagnosis. *Indian J Pediatr* 2018;85:440-7.
8. Desai MP. Disorders of thyroid gland in India. *Indian J Pediatr* 1997;64:11-20.
9. Rama Devi AR, Naushad SM. Newborn screening in India. *Indian J Pediatr* 2004;71:157-60.
10. Sanghvi U, Diwakar KK. Universal newborn screening for congenital hypothyroidism. *Indian Pediatr* 2008;45:331-2.
11. Kishore KR, Ranieri E, Fletcher J. Newborn screening for congenital hypothyroidism in India is overdue. *J Neonatal Biol* 2014;3:129.
12. Zeinalzadeh AH, Talebi M. Neonatal screening for congenital hypothyroidism in East Azerbaijan, Iran: The first report. *J Med Screen* 2012;19:123-6.
13. Rezaeian S, Khazaei S, Hooshmand E, Esmailnasab N. Gender and risk of congenital hypothyroidism: A systematic review and meta-analysis. *Int J Pediatr* 2017;5:6703-12.
14. Silvestrin SM, Leone C, Leone CR. Detecting congenital hypothyroidism with newborn screening: The relevance of thyroid-stimulating hormone cutoff values. *J Pediatr (Rio J)* 2017;93:274-80.
15. Botler J, Camacho LA, Cruz MM. Phenylketonuria, congenital hypothyroidism and haemoglobinopathies: Public health issues for a Brazilian newborn screening program. *Cad Saude Publica* 2012;28:1623-31.
16. Korada SM, Pearce M, Ward Platt MP, Avis E, Turner S, Wastell H, *et al.* Difficulties in selecting an appropriate neonatal thyroid stimulating hormone (TSH) screening threshold. *Arch Dis Child* 2010;95:169-73.
17. Olivieri A, Corbetta C, Weber G, Vigone MC, Fazzini C, Medda E, *et al.* Congenital hypothyroidism due to defects of thyroid development and mild increase of TSH at screening: Data from the Italian national registry of infants with congenital hypothyroidism. *J Clin Endocrinol Metab* 2013;98:1403-8.
18. Korada M, Pearce MS, Ward Platt MP, Avis E, Turner S, Wastell H, *et al.* Repeat testing for congenital hypothyroidism in preterm infants is unnecessary with an appropriate thyroid stimulating hormone threshold. *Arch Dis Child Fetal Neonatal Ed* 2008;93:F286-8.
19. ICMR Task Force on Inherited Metabolic Disorders. Normative data for thyroid stimulating hormone for screening of congenital hypothyroidism. *Indian J Pediatr* 2018;85:941-7.

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