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Dilemmas in neonatal screening for congenital hypothyroidism.

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Abstract

A retrospective analysis of our screening program for congenital hypothyroidism (CH) was done. A total of 553 healthy term neonates were screened on day 4 of life with thyroid stimulating hormone (TSH). Elevated TSH of > 20mIU/L was noted in 10 neonates (1.8%). Two neonates had elevated TSH on retesting but the levels of free T4 and free T3 were normal. No case of permanent CH was noted in this study. The practice of applying day 4 TSH measurement as compared to cord blood TSH measurement and the use of age appropriate cut-off for TSH help to reduce incidence of false positive TSH elevations. We reiterate the need for universal screening of CH in India.

Keywords: Congenital hypothyroidism, Thyroid stimulating hormone (day 4)

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Introduction

Newborn screening for congenital hypothyroidism (CH) began in 1970s and the rationale for such screening is well established. Newborn screening for CH is routinely done in developed countries, while in developing countries a routine screening program for CH is not yet universal. Children with CH are being missed at birth and are often diagnosed late in infancy. We did a retrospective analysis of our neonatal screening program for CH using day 4 thyroid stimulating hormone (TSH).

Material and Methods

Cord blood was used as a screening tool for CH in our hospital till Dec 2012. From Jan 2013 all babies born in our hospital were screened for CH by TSH estimation on venous blood obtained on day 4 of life. All mothers were counseled about the need for screening and informed consent obtained. None of the mothers refused the screening procedure. Preterm neonates (less than 37 completed weeks), birth asphyxia or any illness requiring immediate NICU admission were excluded from the study. TSH analysis was done by Microplate Enzyme Immunoassay. A cut off value of 20mIU/L was taken for initial screening of congenital hypothyroidism. For those with elevated TSH values a repeat ve ous sample for free T4 and TSH was done after 7 days of life.

Results

A total of 612 neonates were born from January 2013 to October 2014. We excluded 59 neonates from the study because of prematurity and NICU admissions for respiratory distress and birth asphyxia. Of the 553 neonates included in the study, 282 were males and 271 were females. Elevated TSH of more than 20mIU/L was noted in 10 neonates (1.8%). TSH levels were within the borderline category (10 – 20mIU/L) in 40 neonates (7.2%). TSH level less than 10mIU/L was noted in 503 neonates (91%). On re-testing of neonates with elevated TSH on day 7 of life, TSH and fT4 levels were normal in 8 neonates. Two of the 10 neonates with elevated day 4 TSH levels (> 60mIU/L and > 40mIU/L) had persistent elevation of TSH (>60mIU/L and 16.78mIU/L respectively) but with normal levels of free T4 (1.15ng/dl and 1.14ng/dl respectively) on day 7 of life. TSH levels were normal when tested at 1 month of age in both of these neonates. Thyroid binding globulin levels, radioisotope thyroid scan or ultrasound of the thyroids could not be done in these neonates.

The TSH values ranged between 0.05 –60mIU/L with median at 2.4mIU/L (IQR = 0.9 – 5.4) {Fig. 1}. The mean TSH level in this study was 4.03±5.29mIU/L. There was no difference in the mean TSH level between males (4.04±4.7mIU/L) and females (4.01±5.9mIU/L). The recall rate for re-testing was 1.8% (10 out of 553 neonates).

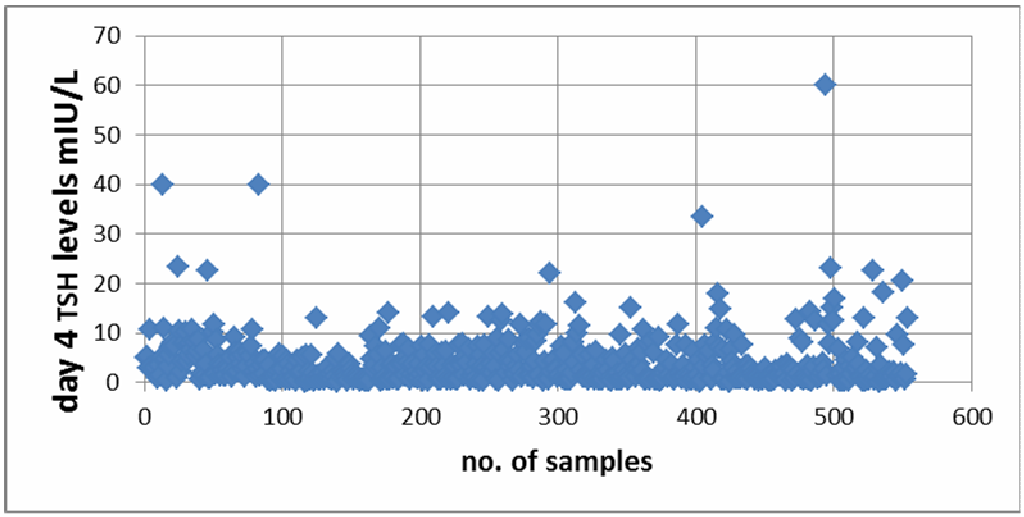

Figure 1. *Scatter plot of distribution of day 4 TSH values*

Discussion

Primary sporadic congenital hypothyroidism (CH) is the most common cause of hypothyroidism in infancy and early childhood in iodine sufficient regions. The worldwide incidence of CH is 1:3000 live births [1] and the estimated incidence in India is 1:2500-2800 live births [2]. The incidence varies depending on iodine sufficiency, laboratory methods, screening practice (changes in test cut offs) demographic, geographic, racial/ethnic and other unknown factors. The incidence across Indian states varies with reports from North India (Chandigarh) 1:3400 [3], (Lucknow) 1:1220 [4], Southern India (Kochi) 1:500 [5], (Chennai) 1:785 [6] and Eastern part of the country 1:600 [7].

Newborn screening for CH has been universally accepted as an essential part of screening for various metabolic disorders. It is successfully implemented in most developed countries, and has proven to be one of the most cost effective screening programs in the field of preventive medicine and public health. The cost benefit ratio is 10:1 along with tremendous clinical impact. There has been a progressive increase in coverage, technological performance, and shortened turnaround time, early reconfirmation of diagnosis, and initiation of treatment, consensus on the dose (10 to 15µg/kg) to be used, periodic follow-up and ultimate outcome [8]. But in India, a national newborn screening program is still not being universally implemented and a treatable cause of mental retardation like CH is being missed.

Majority of screening programs use filter paper TSH collected by heel prick, or T4 followed by back up TSH on days 2 to 5 after birth, when the TSH and T4 levels have normalized following the initial surge in TSH which occurs within 30 min of birth and in T4 within the first 24 h. Many newborn screening programs in North America and Europe measure levels of T4, followed by measurement of TSH when T4 is low. Other neonatal screening programs in North America, Europe, Japan, Australia, and New Zealand are based on a primary measurement of TSH [1].The advantage of primary T4 over TSH screening is that hypothalamic or pituitary hypothyroidism, hypothyroxinemia and thyroid binding globulin deficiency will be missed by primary TSH method. When T4 is checked first milder /subclinical cases of CH will be missed as T4 is initially normal with elevated TSH due to the initial surge during labor. Concomitant measurement of T4 and TSH is the most sensitive approach but incurs a higher cost [8]. Alternately cord blood can be used for screening of CH in situations of early discharge before 3 days [9, 10].

A cut off of TSH greater than 20mIU/L has been validated for suspecting CH [11]. In this study the 95th percentile of TSH was 12.6mIU/L and the 97th percentile of TSH was 14.6mIU/L. Our study found elevated TSH greater than 20mIU/L in 10 out of 553 cases. Thus there was a medical recall rate of 1.8%. Vignesh et al reported a similar recall rate of 1.39% when using the 20mIU/L cut-off, but the recall rate reduced to 0.84% when age appropriate cut-offs were used [4]. We had two neonates (out of 10 recalled) with transient CH whose elevated TSH values returned to age appropriate levels with normal fT4 on further follow up. These cases of transient CH may need long term follow up as studies have found subclinical hypothyroidism in such neonates later on [12]. No case of permanent CH was detected in our study period.

An earlier study from the same institution using cord blood TSH for screening of CH found a higher recall rate of 2.8% (22 out of 785 neonates) and 5 cases of transient CH. There was one case of permanent CH in that study. The TSH levels ranged from 0.08 – 39.2mIU/L with a median at 6.0mIU/L (IQR = 4.0 – 8.5). The mean TSH in that study was 6.9±4.8mIU/L [6]. This was significantly higher than the mean TSH from the present study. Also there was a 36% decrease in the recall rate compared to the study using cord blood TSH. Use of age appropriate levels for TSH will significantly reduce the rate of false positives and the recall rate, hence reducing the overall cost and improving the success of screening program [8, 13].

Conclusion

Screening for CH is essential given the high rates of CH reported in India. Higher recall rates are usually due to transient congenital hypothyroidism which may require long term follow up. Use of age appropriate cut-offs for TSH and fT4 will significantly reduce the incidence of false positives and recall rate.

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