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ORIGINAL ARTICLE

Normative Data of Thyroid Gland Volume in South Indian Neonates and Infants

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Abstract
Objective To establish normative ultrasound data for thyroid gland volume in South Indian neonates and infants and compare with abnormal sonological features of thyroid in congenital hypothyroidism (CH) to explore thyroid ultrasound utility as a supportive screening tool to newborn screening programs for early detection of CH.
Methods In view of impact of geo ethnic factors, varying growth velocities and body mass indices of human population worldwide, specific regional, age and gender related reference data for thyroid gland size and volume are vital. This study was an offshoot of ICMR pilot New Born Screening (NBS) project for CH.

Formula used for thyroid volume estimation was ellipsoidal formula D1 x D2 x D3 × 0.523.

It was a prospective observational study. The neonates who screened negative for Thyroid Stimulating Hormone (TSH) with repeat normal serum TSH and free thyroxine were selected. One hundred fifty seven infants were enrolled which included 99 boys and 58 girls. The study population included children in age groups from 3 d to 1 y six months.
Results Data analysis was done by descriptive method and unpaired t test. Mean thyroid volume was 0.26 ml with 0.27 ml in boys and 0.24 ml in girls. Statistically significant "*p* value" was noted in single lobe measurements among boys and girls.
Conclusions Thyroid gland volume normative data play a key role in evaluation of thyroid sonological abnormalities in CH and there is effective utility of ultrasound as a supportive diagnostic and prognostic screening tool for early detection of CH.

Keywords Ellipsoidal formula · Dyshormonogenesis · Neonatal thyroid volume nomogram · Ultrasound thyroid

Introduction

The most common preventable and treatable endocrino metabolic cause of intellectual disability (ID) or mental retardation in pediatric population is Congenital Hypothyroidism (CH) and currently, worldwide prevalence of CH is estimated to be "1 in 2000–3000" live births as against "1 in 6700" before the era of universal newborn screening [1]. Recent Indian surveys in 325 districts have reported 263 districts as iodine deficiency disorders (IDD) endemic and with a 37% increase in Asian births and significant rise in preterm neonatal births, burden of CH is expected to be several folds more in India [1, 2]. Indian Council of Medical Research (ICMR) National Task Force (NTF) launched pilot multi- centric project for Inborn Metabolic Disorders (IMD) with New Born Screening (NBS) for Congenital Hypothyroidism (CH) and Congenital Adrenal Hyperplasia (CAH) from 2008 to 2012. A total of 20,355 neonates were screened at Chennai centre and final reports show an alarming prevalence of CH at "1 in 727", thereby justifying need for routine screening of all newborns for CH [3, 4].

As per ICMR guidelines of this project, next step in evaluation of confirmed CH positives is to perform sonological examination of thyroid gland. With supportive mass screening

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tools, early detection of CH will further improve clinical outcomes and when resources are limited, utility of ultrasound of thyroid gland among first line of investigations could be further cost-effective and define need for more investigations including scintigraphy [1, 5]. Ultrasound of the thyroid gland is a safe, non-invasive screening method for quantitative assessment of thyroid gland volume most suitable for mass screening in neonates and infants. *Assessment of thyroid gland volume will serve as better indicator of its growth potential than any other linear dimension within gland* [6]. The main application of sonology of thyroid gland lies in its utility to assess position, size and volume of thyroid gland, diagnose type of CH, predict outcome and establish prognostic factors. Sonologically detected abnormally enlarged thyroid glands, hypoplasia and absence of thyroid gland in normal neck position are being recognized increasingly.

Due to geo ethnicity, age and gender related physiological factors in thyroid functions and body mass and growth velocity differences among various populations worldwide, regional scales of measurement and methodology become necessary [1–3, 5]. Statistical applicability of any data will be complete only when normative data are available for comparison. This study on normative data of thyroid gland volume by ultrasound is first of its kind in newborns and infants in South India and results will be pivotal for effective management of CH.

Material and Methods

Study objective was to establish baseline normative reference data for thyroid gland's size and volume by sonological examination of thyroid gland in neonates and infants belonging to South Indian population who were biochemically and clinically euthyroid and to evaluate its applicability by comparing with abnormal sonological findings in congenital hypothyroidism (CH) affected neonates to explore thyroid ultrasound utility as a supportive screening tool in mass newborn screening programs. Target population belonged to ICMR pilot project and was an offshoot study initiated by Fetal Care Research Foundation (FCRF) and followed up at Pediatric and Endocrine clinic. Study period *was t*wo years with data collection for 1 y and six months and follow up for six months. Study population included neonates and infants from 3 d of age to 1 y. Study design was prospective and observational. After obtaining institutional ethical committee approval and informed written consents from parents of screened neonates study participants recruitment was decided based on biochemical reports of neonates and who tested screen negative for TSH values were included in the study. These neonates were recalled and after detailed information regarding study purpose was explained, written consents were obtained. A detailed history and clinical evaluation was performed by a qualified Pediatrician and assisted by a trained staff nurse. Serum thyrotropin or TSH and free thyroxine levels were done and those newborns with negative tests for CH in both initial screening and repeat confirmatory serum tests and clinically normal with no known family history of thyroid related disorders were enrolled in the study. Inclusion criteria were ages from day 3 to 1 y six months of age with gestational ages at term 37 wk to 42 wk, birth weight 2500 g and above and singleton babies. Exclusion criteria were refusal of consent, preterm babies, low birth weight babies, multiple gestations, neonates with congenital anomalies, mothers and family members having thyroid disorders.

Instruments used include real time sector scanner transducer frequency 9–10 MHz pediatric probes. Position of patient was hyper extended neck position in supine and posture measurement planes were antero posterior and transverse. Width, length, breadth and depth of each lobe were measured and volume of each lobe was calculated using ellipsoidal formula for thyroid volume calculation, "*Volume in ml = D1 x D2 x D3 x 0.523,*" *in which Long axis diameter of each lobe = D1, Short axis = D2, Thickness of each lobe = D3.* Each lobe volume was calculated as right and left and average was noted as mean thyroid volume (MTV). *Combined mean thyroid volume was calculated as* ***MTV (ml) = RTV + LTV /2.*** *If each lobe is considered as an ellipsoid, much of the contribution of the isthmus is already included. Hence, individually isthmus is not included in volume calculations* [6].

Results

Statistical analysis was done using SPSS version 20. Descriptive statistics was used to describe mean values in relation to different age groups and gender. "Unpaired t test" was used to compare mean values between boys and girls and among different age groups. "*p* value" less than 0.05 was considered as statistically significant.

Age groups were divided into 3 to 15 d and 16 d to 30 d for neonates. Subsequently, analysis was done in age group 3 d to 1 mo and 2 to 3 mo. Comparative group statistics were further done for age group 7 to 9 mo, 10 to 12 mo, 13 to 15 mo and 16 to 18 mo respectively. For age groups, ranges 13 to 15 mo and 16 to 18 mo, values of MTV were 0.30 and 0.51 in boys and MTV in girls were 0.24 and 0.32 ml respectively. When age groups were considered, statistical analysis showed that there was no significant difference in the mean thyroid volumes between age groups 1–30 d and 2–3 mo with a *p* value of 0.328 (CI 95% - 0.01818 to 0.05384).

In Table 1 mean thyroid volume (MTV), right thyroid volume (RTV) and left thyroid volume (LTV) are tabulated across different age groups. MTV in milliliters for study sample (N = 157) was 0.264(SD = 0.97) with a minimum of 0.12 ml and maximum of 0.75 ml.

Table 1 Agewise grouped thyroid gland volume (TV) in milliliters with mean, median and SD

Age/	RTV (ml)			LTV (ml)			MTV (ml)		
	Mean	Median	SD	Mean	Median	SD	Mean	Median	SD
03–15 d	0.27	0.24	0.12	0.23	0.24	0.07	0.25	0.24	0.09
16–30 d	0.26	0.25	0.09	0.26	0.22	0.11	0.25	0.22	0.09
01–03 mo	0.24	0.22	0.08	0.23	0.21	0.07	0.23	0.22	0.07
04–06 mo	0.31	0.29	0.10	0.26	0.22	0.10	0.28	0.26	0.09
07–09 mo	0.28	0.25	0.13	0.28	0.25	0.10	0.28	0.25	0.11
10–12 mo	0.26	0.26	0.05	0.24	0.23	0.06	0.25	0.25	0.05
13–15 mo	0.29	0.29	0.10	0.28	0.28	0.11	0.28	0.26	0.10
16–18 mo	0.45	0.38	0.19	0.41	0.33	0.20	0.43	0.32	0.19

LTV Left thyroid volume; *Med* Median; *ml* In milliliters; *mo* Months; *MTV* Mean thyroid volume; *RTV* Right thyroid volume; *SD* Standard deviation

MTV for boys was 0.274 ml with SD 0.102 and in girls MTV was 0.247 ml and a SD of 0.086.

In Table 2, mean values and individual lobes of thyroid gland volume among boys and girls are described. No statistically significant difference was found in mean thyroid volumes between boys and girls, 0.274 and 0.247 respectively with a *p* value 0.095. But there was a significant difference in *p* value less than 0.05 in left lobe thyroid volume of boys compared to girls with *p* value at 0.016.

Discussion

Ultrasound imaging is a reliable method for estimation of thyroid size and volume in workup of neonates suspected to have CH [1, 6]. In transient TSH elevation, thyroid gland should be of normal size and volume. In true congenital hypothyroidism (CH), ultrasound may show absence of thyroid gland in the normal neck position which could be due to either ectopia or agenesis. The detection of a small thyroid gland can occur in hypoplasia or it is enlarged with or without a neonatal goiter in dyshormonogenesis [1, 5, 6].

In this pilot study on Indian neonates and infants, mean thyroid volume (MTV) was 0.264 ml. In another study report by Ueda [6], mean thyroid volume of term neonates were within range of 1.20 ml to 1.60 ml with an average of 0.76 ml respectively. Similar normative study in Germany reported MTV of 1.1 ml [7]. Otten has reported thyroid volume values from one month of age to one year of age as 0.30 ml to 1.70 ml [8]. A study from Turkey by Mutlu et al. has reported analyzing thyroid gland volume in newborns by associating with thyroxine, triiodothyronine levels and TSH in cord blood and serum samples and MTV was 0.72 +/− 0.24 ml in term neonates [9].

A lesser volume in this study could be partly due to ethnic factor of shorter length or height of Indian population as height is the most important anthropometric measure deciding thyroid volume. In addition to lesser mean thyroid volume, another significant feature noted in index study was that mean thyroid volume correlations in both boys and girls were not statistically significant. An explanation could be that in neonates and infants, body surface area and length of babies are not significantly different in boys and girls. But individual thyroid lobe measurements, both right and left lobes, in girls

Table 2 Thyroid lobes volume in males and females

Variables	Mean	S. D.	t-value	*p*-value	95 % CI Lower and Upper Limits
Right Lobe Thyroid Volume					
Males (N = 99)	0.2813	0.11453	0.947	0.345	−0.01827, 0.05193
Females (N = 58)	0.2645	0.09405			
Left Lobe Thyroid Volume					
Males (N = 99)	0.2723	0.10324	2.445	0.016	0.00784, 0.07371
Females (N = 58)	0.2316	0.09655			
Mean Thyroid Volume					
Males (N = 99)	0.2743	0.10251	1.682	0.095	−0.00470, 0.05856
Females (N = 58)	0.2474	0.08622			

CI Confidence interval (Lower and Upper limits); *N* Number of participants; *p value* Probability value; *S.D.* Standard deviation; *t value* t test

infants had a "*p*" value of less than 0.005 (statistically significant) when compared to boys. As per reports published by Ueda and Klingmuller, male children usually have right lobes larger than female children [6, 8]. In general, boys and girls have same thyroid volume till around 8 y of age and after puberty occurs, changes usually occur accordingly [6, 7].

A study in Polish newborns provided normative data on volumes for right lobe, left lobe, and both lobes combined and were 0.502 (range, 0.228–0.931), 0.511 (range, 0.294–0.959), and 1.014 ml (range, 0.526–1.849) respectively. The World Health Organization bases its reference standards for normal thyroid volumes on values derived from measurements of European children using the ellipsoid formula. However, studies have shown that thyroid size is not only related to iodine intake and disease factors but also related to other factors, such as a child's race, region, age, height, and weight; Differences in thyroid volume may also be due to goitrogens, inadequate iodine intake, use of different formulae for estimation and seasonal variations, in that during winter, thyroid volume increases to about 23% [10].

The criteria for definition of goiter as per WHO is a thyroid volume above 97thpercentile of the reference population [11]. The reference value of thyroid volume is necessary to determine goiter prevalence and it is important that which value will be considered as normal. As this study is a pilot study and it included only normal infants, values are expected to be normal and there is lack of reference data to compare and comment on which value is normal or abnormal.

An attempt has been made to define percentiles based on normative results in this study and a comparison with thyroid volumes in CH confirmed newborns was possible.

For male infants, 25th percentile was at 0.21 ml with 99th centile at 0.75 ml, while in females, it was 0.19 ml and 0.59 ml, respectively.

Patients identified with CH in ICMR pilot study results at Chennai centre have revealed small volumes in hypoplastic glands up to 0.05 ml and larger volumes up to 1.45 ml have also been documented in neonates with and without goiter due to dyshormonogenesis.

Limitations in index study include small sample size, unavailability of Indian studies in neonates and infancy to compare and correlate, lack of data on urinary iodine of study population and study on effect of goitrogens. Therefore it is vital to analyse large sample sizes of Indian populations. A study from Philippines has reported thyroid volumes smaller than the reference data of WHO/ICCIDD in 1997 [11, 12]. The reference was based on Europe which is an iodine deficiency area. When compared with other reports from iodine-sufficient areas, thyroid volumes of Philippines study were smaller than other studies by age, but similar to other studies by body surface area. It was concluded that reasons could be because weights and heights of children in Philippines are smaller than other countries. But paucity of data of weight and height by age in other studies was a limitation. Therefore World Health Organization recommends that normal values for each region be estimated separately [11].

There is a need to establish specific local values in any population with adequate iodine intake. Correct interpretation of ultrasonography also relies on the availability of standardized reference criteria from populations whose iodine status is known to be adequate. Since thyroid size varies by age, body height and weight derivation of normative values intended for universal application needs to be based on both these variables.

Conclusions

This study is first of its kind among Indian neonates and infants and technically defining thyroid gland size and volumes are difficult in this age group. With increasing numbers of CH affected newborns detected by Newborn Evaluation by Spot Test, "*NEST*" screening program, ultrasound of thyroid gland will play a key role as a supportive mass screening tool to evaluate etiology, outcomes and prognosis of congenital hypothyroidism (CH), the most common preventable and treatable cause of mental retardation in children.

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Conflict of Interest None.

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