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ROLE OF EARLY THYROID SCINTIGRAPHY IN CONGENITAL HYPOTHYROIDISM - A SINGLE CENTRE STUDY

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ABSTRACT

Purpose: Congenital hypothyroidism can cause severe neurodevelopmental morbidity if left untreated, hence early detection and prompt treatment are required for optimizing long-term outcomes. Thyroid scintigraphy is one of the accurate tests for diagnosing primary hypothyroidism.

METHODS: Prospective study was conducted at a tertiary referral Institute in Malabar region, Kerala, India over the period of 3 years from January 2016 to December 2018.

RESULTS: Among 6035 babies screened, 26 babies had CH. Among them 4 of them had agenesis/ectopic thyroid, 3 babies had normal iodide trapping, 18 babies had eutopic thyroid gland with increased uptake and 1 baby had decreased uptake on scintigraphy. On further analysis, 4 out of 5 preterm babies had eutopic thyroid gland with increased uptake and 1 baby had agenesis.

CONCLUSION: Thyroid scintigraphy helps in early and etiological diagnosis of Hypothyroidism. Lowering the cut-off values of hypothyroidism increases the pick-up rate, early diagnosis and initiation of treatment, thus improving long-term outcomes.

1 INTRODUCTION

Thyroid hormones play a crucial role in early neuro-development and hence its important to identify congenital hypothyroidism (CH) early. If left untreated, it results in neurological and psychiatric deficits, including intellectual disability, spasticity, and disturbances of gait and co-ordination. CH is one of the most common preventable causes of mental retardation. The etiology of congenital hypothyroidism (CH) may be important in determining disease severity, outcome and treatment schedules because athyroid patients need higher treatment doses and close monitoring particularly early in life. The aim of this study is to identify the incidence of CH in the study population and to evaluate thyroid scintigraphy (TS) findings prior to treatment.

Though technetium scan is one of the most accurate tests in diagnosing the etiology of primary hypothyroidism, many times it cannot be done due to unavailability of facility or financial constraints.

Based on data from the initial screening programs in the 1970s, it has been accepted that in iodine-sufficient parts of the world congenital hypothyroidism is caused by a defect in thyroid gland formation (dysgenesis) in about 85% of cases, by intrinsic defects of thyroid hormone synthesis (dyshormonogenesis) in the remaining 15%, and rarely by other causes (e.g., maternal TSH receptor-blocking antibodies, iodine deficiency or excess) [2]. The recent changes in patterns of diagnosis have, however, modified the historical distribution of congenital hypothyroidism etiologies in many developed countries. Some recent studies have shown that only 58–69% of permanent congenital hypothyroidism cases are caused by thyroid dysgenesis. The remaining 31–42% of patients have a eutopic thyroid gland consistent with possible dyshormonogenesis [3,4,5]. Recent data have begun to shed light on new genetic causes of dyshormonogenesis in some of these patients.

In a review of newborn screening strategies for congenital hypothyroidism around the world, Ford and LaFranchi [1] found that lowering the TSH cut-off from greater than 20–25mIU/l to greater than 6–10mIU/l in six national newborn screening programs resulted in a 2.2-fold increase in the average incidence of congenital hypothyroidism (from 1 : 3264 to 1 : 1464).

The Indian Society for Pediatric and Adolescent Endocrinology (ISPAE), in 2018 recommended that , in India, screening should be done for every newborn using cord blood, or postnatal blood, ideally at 48 to 72 h of age. On this screen sample, neonates with TSH>20 mIU/L serum units (or >34 mIU/L for samples taken between 24 to 48 h of age) should be recalled for confirmation. ISPAE recommended that preterm and low birth weight infants should undergo screening at 48-72 h postnatal age. Sick babies should be screened at least by 7 d of age. Venous confirmatory TSH >20 mIU/L before age 2 wk and >10 mIU/L after age 2 wk, with low T4 (<10 g/dL) or FT4 (<1.17 ng/dL) indicate primary CH and treatment initiation. Imaging is recommended by radionuclide scintigraphy and ultrasonography after CH is biochemically confirmed but recommends that treatment should not be delayed till scans are performed [8]

In our study, we reviewed the early scintigraphy findings of all the babies, both term and preterm babies, confirmed to have CH biochemically.

2 METHODS

This Prospective study was conducted at a tertiary referral Institute in Malabar region , Kerala, India over the period of 3 years from January 2016 to December 2018.

Delivery details and screening values were obtained from hospital digital records . Follow up was done by Outpatient appointment and / or Telephonic conversations. Our management protocol was based on recommendations by LaFranchi et al and ISPAE recommendations [1,8]

During this period , a total of 6035 babies were screened . All babies were screened for cord blood TSH and fT4 evaluated using chemiluminescence methods . Initial screening cut off value for TSH was taken as value above 8 mlIU/l [3,6,7].

Babies with mildly elevated screen TSH (between 8 and 40 mIU/L) were recalled early in the second week of life (Day 12 - 14 of life) for a repeat screening TSH and Free T4 and those babies with high initial screening TSH >40 mIU/L had a repeat venous confirmatory sample (TSH ,FreeT4) at 72 h of age [24,25].

Babies with TSH values of >40 mlIU/l in the confirmatory testing had their USG neck and thyroid scintigraphy done and commenced on treatment [1,8]. Babies with borderline TSH values (between 8 and 40 mIU/L) at confirmatory testing had another repeat venous sample tested at 3 weeks. After 3 wk of age, if TSH remains persistently >10 mIU/L, USG neck and

thyroid scintigraphy done and commenced on treatment [1,8].

In preterm babies , initial cord blood sampling was done and a repeat TSH sampling, even if the cord sample was normal, was taken at 2-3 weeks as there is often delayed response [9,10]. In our institute, all antenatal mothers are screened routinely for thyroid status.

Ultrasound neck was done by the consultant radiologist to detect the presence or absence of thyroid gland in the neck. Technetium Scan was done in the department of nuclear medicine, 1 -1.5 mci of 99m sodium pertechnetate was injected intravenously and 20 minutes later static images were obtained in anterior, left anterior oblique , right anterior oblique and chest projections. The results of TFT, Ultrasound neck, technetium scan were analyzed using statistical software.

2.1 Statistical Analysis

Data was coded and analyzed using SPSS software (Ver 2.0). Categorical data was presented as frequency and percentage, while continuous data are presented as mean values. Chi-square test was used to determine the association of categorical variables. A p-value of <0.05 was considered significant

3 RESULTS

In this study, we assessed the incidence of CH in a single tertiary post graduate training institute in Malabar region, Kerala , India and also the etiological diagnosis based on thyroid scintigraphy.

A total of 6035 babies were screened based on inclusion criteria over the study period. We had a total of 586 babies who had a screening TSH value of >8 mlIU/l. All except 2 among the 586 babies were able to follow up and 26 babies were noted to have hypothyroidism. Among the study population , there were 18 perinatal deaths but their cut off TSH values were <8 mIU/L.

The incidence was noted to be one case per 232 newborns which is about 10 times higher than that reported from America and Europe [11] . It is similar to a study by Anand et al, in the same region [12] . Various studies in India has shown the incidence ranging from 1:3400 to 1:1042. This difference is noted to be due to different cut off values for TSH [8] . Among the 26 babies, who had CH, 21 babies were term and 5 were preterm.

During this period , we had a total of 512 preterm deliveries and 5523 term deliveries. Hence the incidence was noted to be 1 in 102 for preterm deliveries as compared to 1in 263 for term deliveries.

In our study , We had a total of 17 babies who had initial TSH screening value between 8 and 40 mlIU/1 . On further analysis, we had 9 babies who had TSH values ranging between 8 and 20 mlIU/1 , with lowest being 9.57 mlIU/1. 3 of these babies were preterm and 6 babies were term. There were 8 babies who had TSH values between 20 to 40mlIU/1. 2 of these babies were preterm and 6 babies were term.

For all these babies, when TSH was repeated at 2 weeks , values were between 20-40 mlIU/1 and on scintigraphy had eutopic thyroid with increased uptake. 3 babies, who had raised TSH values of between 10 - 20 mlIU/1 at 2 weeks, had normal uptake on scintigraphy. Among these 3 babies with normal uptake , one baby had normal FT4 with TSH value of 12.73 mlIU/1 at 14 days and hence was not started on thyroxine replacement and levels normalised by 1 month. 2 other babies required thyroxine at very low doses.

Among the 26 babies with CH, 4 babies had agenesis/ectopic thyroid , 3 babies had normal iodide trapping , 18 babies had eutopic thyroid gland with increased uptake and 1 baby had decreased uptake on scintigraphy [Tab :1]. On further analysis , 4 out of 5 preterm babies had eutopic thyroid gland with increased uptake and 1 baby had agenesis. In term babies , 15 babies had eutopic thyroid gland with either increased (14 babies) or decreased uptake(1 baby), 3 babies had eutopic thyroid gland with normal iodide uptake and 3 babies had dysgenesis (2 sublingual and 1 lingual thyroid) [Fig 1].

USG thyroid was able to identify all 4 cases of agenesis or dysgenesis. 1 baby had mildly enlarged thyroid , who had increased uptake on scintigraphy. All the other babies had normal ultrasound scans [Fig 2]

4 DISCUSSION

Understanding the etiology of congenital hypothyroidism may be very important. The rationale for performing early imaging of the thyroid gland is to determine the underlying etiology of CH [16] and to anticipate whether it would be transient or permanent [17]. The higher prevalence of CH with a eutopic thyroid gland [16,18] may be because of increased screening of patients at higher risk (those with very low birth weight or premature infants), a higher detection rate, and the introduction of progressively lower TSH cutoffs [3,19,20]. A recent study by Oron et al in Israel, found out that eutopic thyroid gland and dyshormonogenesis as the most common cause in their population (59%) .Among CH with eutopic thyroid gland, increased uptake was noted in 21.1 % and 37.9% had an intact gland with normal or decreased Uptake [15]. In a French cohort of 32 congenital hypothyroidism patients with a eutopic thyroid gland, Castanet et al. [23] identified transient congenital hypothyroidism in 38%, permanent congenital hypothyroidism in 38%, and persistent subclinical hypothyroidism in 25%. Of note, Castanet et al. included only patients with 'unexplained' congenital hypothyroidism, excluding those with defects of iodine organification documented by a perchlorate discharge test. In addition, they excluded children born preterm, so this data may not apply to this important population of congenital hypothyroidism patients.

However , the actual utility of early radioisotope scintigraphy may have its own challenges. Oron et al [15] has shown that it was inconsistent in predicting the overall outcome in patients with a eutopic gland (irrespective of the radioisotope uptake level, whether increased, normal, or decreased) and did not influence decision making along the clinical course [21]. Although radioisotope scintigraphy with 99mTc is the most sensitive and reliable modality in diagnosing athyrosis or ectopic thyroid tissue [22], it has several pitfalls. Absence of uptake by a eutopic gland may occur upon transfer of maternal TSH receptor-blocking antibodies to the fetus or with exposure of the newborn to exogenous iodine.

Olivieri et al. [5] has reported that preterm infants accounted for about 50% of the total increase in congenital hypothyroidism incidence observed in Italy between 1987 and 2008.

In our study, we have identified a significantly higher incidence of congenital hypothyroidism , which resonates with a similar study by Anand et al in the same geographical area. Geographically, the main population in our study area is from the coastal belt of Malabar region. None of the mothers of neonates with CH had a history of antithyroid drug intake but blocking antibodies were not measured, this was a limitation in our study. The higher incidence may be due to the fact that we have used a lower cut off for screening TSH compared to other studies. 9 babies (6 term and 3 preterm) had initial TSH screening values between 8 and 40 mlIU/l, who later turned out to have CH . Other variables such as environmental, genetic, ethnic variation and familial factors may have involved an increased prevalence rate of CH [13,14].

Early scintigraphy was helpful in establishing an etiological diagnosis, though it didn't have an impact on decision making in general. Only one baby , who had borderline TSH value of 12.73 mlIU/l at 2 weeks with normal FT4 and normal scintigraphy was not started on treatment. This baby's values normalised by 1 month of age. However, it was very helpful in parent counselling and compliance to treatment. This is of great importance in congenital hypothyroidism as this would require long term treatment for at least 3 years.

Follow up studies are required to assess whether these babies with eutopic thyroid gland were transient or permanent CH Based on our finding, we suggest that further multicentric prospective studies need to be undertaken in the region and also to identify factors that may cause higher prevalence of CH in our community within the next few years.

Acknowledgements

Table 1. Table showing the scintigrapgy results Frequency vs Percentage

Scitigraphy	Frequency	Percent
Decreased iodide trapping	1	3.8
Increased iodide trapping	18	69.3
Normal iodide trapping	3	11.6
Lingual thyroid	1	3.8
Sublingual	2	7.7
Agenesis	1	3.8
Total	26	100

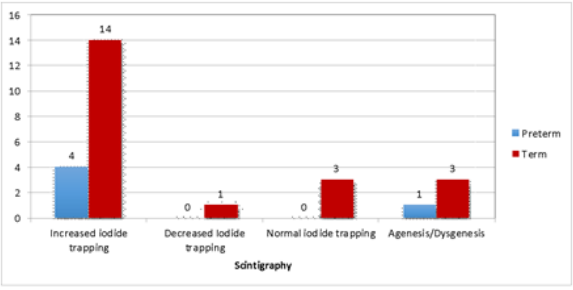

Fig. 1. Preterm v/s Term on etiology based on scintigraphy

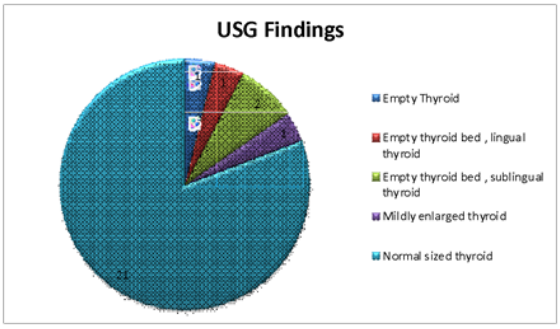

Fig. 2. Ultrasonography findings and Thyroid abnormality percentages.

Abbreviation

CH – Congenital Hypothyroidism
TS – Thyroid Scintigraphy

Key messages

What is Already Known? The incidence of CH has risen over the last few decades, largely because of changes in newborn screening strategies, shifting emographics, and the increasing survival of preterm infants

What this Study Adds?

Our study shows the importance of lower cut off values for screening CH and the role of early scintigraphy in identifying the etiological diagnosis which helps in better parent counselling as well as compliance

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