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*Research Article*

# The Role of Thyroid Scintigraphy in Infants with Congenital Hypothyroidism: Our Experience at Royal Hospital, Oman

**Asya S. Al-Busaidi[1], Naima K. Al-Bulushi[2]*, Khalsa Z. Al-Nabhani[2]**

[1]*Nuclear Medicine Fellow, University of Ottawa, Canada.*
[2]*Nuclear Medicine Department and Molecular Imaging Center, Royal Hospital, Oman.*

## Corresponding Author Information

Naima K. Al-Bulushi

Nuclear Medicine department and molecular imaging center, Royal Hospital, Muscat, Oman.

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## ABSTRACT

**Objectives**: The early diagnosis and treatment of congenital hypothyroidism is critical, to avoid detrimental outcomes such as mental retardation. Thyroid stimulating hormone (TSH) level is the usual diagnostic screening test; however, thyroid scintigraphy helps identify etiologies of the disease there by determining different management plans. The aim of this descriptive retrospective study is to evaluate thyroid scintigraphy findings in newborns and children with biochemical evidence of congenital hypothyroid and to assess the impact of thyroid scintigraphy findings on the long-term management of those patients.

**Methods**: Retrospective review of 101 infants with congenital hypothyroidism (CH) who were initially diagnosed biochemically, and then underwent thyroid scintigraphy, between 2010 and 2015 at a tertiary hospital in Oman. Patients' data was collected from the hospitals' database and then analyzed using statistical package for social sciences (SPSS).

**Results**: 8.9 % (9/101) patients had the thyroid scintigraphy up to 7 days of life, whereas 91.1% (92/101), were performed after the age of 3 years. The performed scintigraphy revealed five different findings which included dyshormonogenesis, ectopia, agenesis, reduced and normal % of Tc-99m pertechnetate uptake in the thyroid gland. The most common cause of congenital hypothyroidism in this cohort was ectopic sublingual thyroid, 32.6% (33/101), and the ratio of female to male was 1.29:1, in keeping with international figures. However, in this cohort the Dyshormonogenesis was the cause of congenital hypothyroid in 29.7% (30/101) patients, which is higher than that known internationally and can be probably attributed to the high rate of consanguineous marriage in the country.

39.6% (40/101) patients required alteration in management (increase or decrease thyroid hormone dosage, start, or discontinue the treatment) based of thyroid scintigraphy, US and serial TFT. There was a statistical significance (p-value= 0.000) between scan findings and the need to change the treatment plan following the scan.

**Conclusion**: Thyroid scintigraphy is an essential part of screening program for congenital hypothyroidism and useful in differentiating the causes of congenital hypothyroidism thus essential for proper management plans. We, therefore, highly advise to increase the awareness of early utilization of thyroid scintigraphy in congenital hypothyroidism screening.

## Keywords

Congenital hypothyroidism, Thyroid scintigraphy, Tc-99m pertechnetate, Neonatal hypothyroidism.

## Introduction

Hypothyroidism is defined as insufficient production of thyroid hormone, which can be due to primary gland failure, insufficient thyroid gland stimulation by the hypothalamus or iatrogenic. The main causes of primary gland failure are congenital abnormalities, autoimmune disease such as Hashimoto, iodine deficiency and infiltrative disease [1]. Congenital hypothyroidism (CH) has an incidence of 1 in 3000-4000 births worldwide with some ethnic variation in frequency affecting females more than males [2,3]. It can be a transient abnormality resulting from fetal thyroid suppression by maternal antibodies or a mild form of dyshormonogenesis [4-6]. Transient congenital hypothyroidism has been reported with an incidence as high as 25%, hence identifying such cases allows safe discontinuation of thyroxine replacement therapy later [7].

Early detection and treatment of CH can prevent long-term sequel of physical and mental retardation (cretinism), therefore a screening program for CH has been established in Oman since 2004. Congenital hypothyroidism is detected by cord blood screening of thyrotropin levels (thyroid stimulating hormone; TSH). Elevated values are further confirmed with TSH levels in newborn venous blood, once confirmed, thyroxine replacement therapy is immediately instituted. As per the national guidelines, the cutoff levels for CH diagnosis based on TSH are cord blood levels above 40 mU/L, serum blood value above 20 mU/L on days 1- 6 and above 10 mU/L on day 7 [2]. Newborns with TSH above the cutoff point are further evaluated by thyroid imaging with ultrasound, scintigraphy, and adjunctive measurement of serum thyroglobulin (Tg) to establish the causes of CH preferably within the first 7 days of life [8-10].

While thyroid ultrasound is used to evaluate the presence verses the absence of thyroid gland in the normal anatomical location, thyroid scintigraphy, using isotopic iodide ($^{123}$I) or Technetium 99m pertechnetate, provides information on the structure of the gland as well as its function [11].

It should be clearly expressed that thyroid scintigraphy does not diagnose transient hypothyroidism, but it can help to identify the two subgroups among whom it is prevalent, that is, aplasia and dyshormonogenesis. In children of these groups after the critical period for brain damage has passed, at age 3 years, thyroxine is carefully and briefly withdrawn to evaluate whether the neonatal hypothyroidism in each patient was transient or permanent and to determine the need for lifelong therapy, genetic counselling, and the target genetic investigations, particularly for enzymatic disorders [12].

The aim of this descriptive retrospective study is to evaluate thyroid scintigraphy findings in newborns and children with biochemical evidence of congenital hypothyroid and to assess the impact of thyroid scintigraphy findings on the long-term management of those patients. An ethical approval was obtained from the Royal hospitals research committee.

## Methods

Newborns and children who were biochemically diagnosed with congenital hypothyroid and underwent a thyroid scintigraphy between years 2010-2015 at a tertiary hospital in Oman (Royal Hospital) were included in this study. A Data collection sheet with variables was designed for all patients, including hormonal levels, thyroid scintigraphic findings, ultrasound scan findings, age when radioisotope scan was performed, change in management and outcomes in terms of any long-term complications. The hospital database system was used to obtain the data and trace the reports of the thyroid scans and other information. These scans were reported by a dually certified radiology and nuclear medicine physician. The images have been retrieved from the Picture Archiving and Communications System (PACS). Laboratory results, clinical data, and original descriptions of ultrasound and radioisotope scans were retrieved from the Hospital Information Support (HIS). Verified information was collated on an excel spreadsheet. Ultrasound and thyroid scintigraphy images were reviewed by a radiology resident, who was blinded as to the previous diagnosis but allowed to view both images simultaneously. Final diagnosis was agreed based on combined clinical evaluation, biochemistry, and thyroid imaging findings.

Data was analyzed using SPSS 22 where the categorical variables were outlined in frequency percentages and the Pearson Chi square test was performed to interpret clinical significance, with a p-value of $<0.05$ considered to be significant.

### Imaging Technique/Protocol

On the day of thyroid imaging, an intravenous cannula is inserted to facilitate injection of technetium-99m pertechnetate. The infant / child is then fed to diminish salivary gland activity and to calm them down; in order to reduce movement artifacts. The amount in megabecquerel (MBq) of intravenously administered radiotracer is dependent on infant's weight.

Fifteen to twenty minutes after injection, anterior and lateral scans are obtained with the neck in extension position by means of a support under the back of the chest and shoulders. Each view was acquired for a 5-min period. The images included the entire field from head to chest, where the extended head was supported and held in place manually, usually by the parent, together with scans that included a cobalt marker to localize the suprasternal notch and nose. The scan is carried out using a gamma camera (SIEMENS Dual head SPECT EVO) with a low energy high-resolution parallel collimator, imaging matrix of 256 x 256 and a zoom of 3.2. Visible uptake in salivary glands indicated adequate isotope application. The presence, position of uptake, symmetry, homogeneity, and avidity of radiotracer absorption were recorded. The normal limit of Tc-9m pertechnetate uptake in thyroid scintigraphy was (0.4 % - 4 %).

## Results

Hundred and one children with biochemically diagnosed congenital hypothyroidism who had undergone a thyroid scintigraphy at our institution between 2010 and 2015 were

included in this study. Their age at diagnosis ranged between 1 day and 11 years old while their age at the time of scan was 2 days to 12 years old, out of which 56.4% (57/101) were females, the female to male ratio was 1.29:1, in keeping with international statistics on the epidemiology of congenital hypothyroidism being higher in females [14]. Only 8.9 % (9/101) of this cohort had the thyroid scintigraphy done within their first 7 days of life, the majority of the scans, 91.1% (92/101), were performed after the age of 3 years. Unfortunately, in this population there were 18.8% (19/101) patients with mental retardation secondary to delayed diagnosis and treatment of congenital hypothyroid.

Five patterns of thyroid scintigraphy were recognized and these determined patient classification: (i) normal in 24.7% (25/101) patients (Figure 1); (ii) ectopia in 32.6% (33/101) children requiring lifelong thyroxine replacement therapy (Figure 2); (iii) reduced thyroid uptake in 5.9% (6/101) patients who then discontinued thyroxine replacement therapy (iv) agenesis was found in in 6.9% (7/101) of them (Figure 3); and (v) dyshormonogenesis, in which there is markedly increased technitium-99m pertechnetate concentration, in 29.7% (30/101) patients (Figure 4) [13].

On following up the clinical visits' registry of the patients in this cohort, it was found that 39.6% (40/101) of them required an alteration of their management (increase/decrease in thyroid hormone dosage or start/discontinue treatment). Only a small percentage of those diagnosed with dyshormonogenesis required a change in management, 8.9% (9/30). However, 52% (13/25) of those with a finding of a normal thyroid scintigraphy scan required to discontinue their treatment and 54.5% (18/33) of those with a finding of an ectopic thyroid gland required to increase their administered doses, the figures are statistically significant with p-values of < 0.001. The change of management decision was made based on combining the thyroid scintigraphy's findings with that of the thyroid ultrasound, clinical evaluation, and serial thyroid function test results (Diagram 1).

The most common cause of congenital hypothyroidism in this cohort was ectopic sublingual thyroid gland, 32.6% (33/101), in keeping with international figures of anatomical defects (thyroid dysgenesis) being the most common cause of congenital hypothyroidism.

## Discussion

Congenital hypothyroidism is mostly a permanent disorder requiring lifelong thyroxine replacement therapy. However, in 25 % of newborns diagnosed with CH at birth this disorder is transient and thyroxine replacement can be stopped at a later stage in life [7]. The main causes for permanent congenital hypothyroidism are thyroid dysgenesis (aplasia, hypoplasia or ectopia), thyroid hormone biosynthetic defects (also known as dyshormonogenesis), iodine deficiency (endemic cretinism) and hypothalamic-pituitary hypothyroidism.

On the other hand, it may be transient of which the main etiologies are; TSH binding inhibitory immunoglobulins, Exposure to goitrogens (iodides or antithyroid drugs), Transient hypothyroxinemia of prematurity and sick euthyroid syndrome [15]. While most congenital hypothyroidism cases are due to sporadic

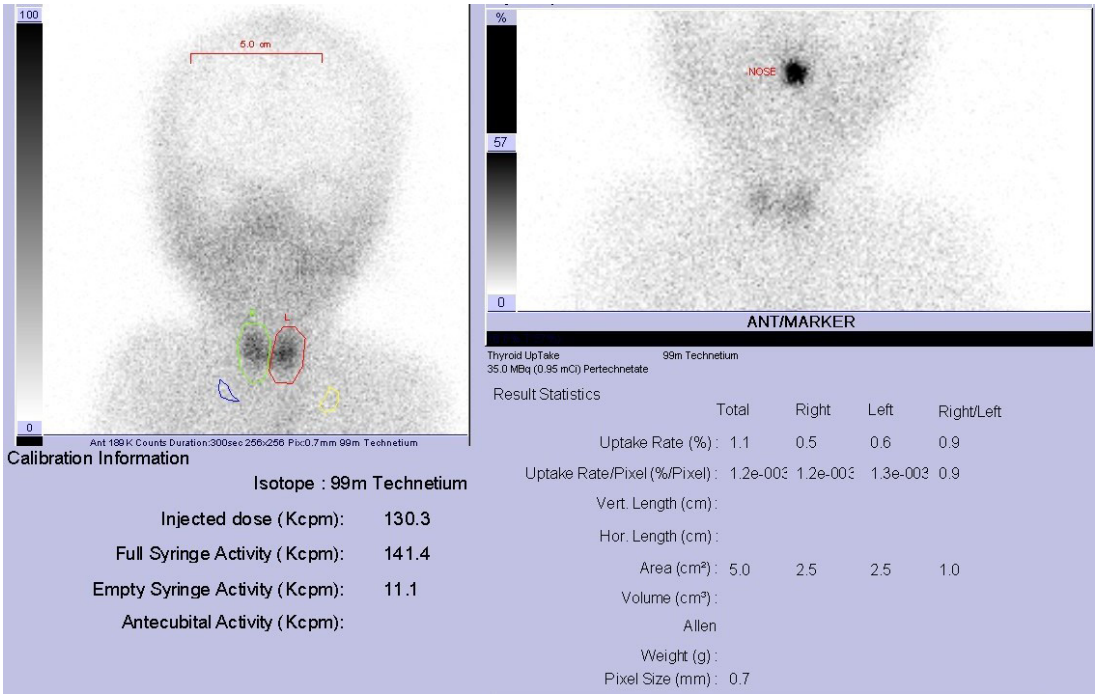


**Figure 1:** Tc-99m pertechnetate Thyroid scintigraphy in a newborn female with elevated cord blood and serum TSH level. The % of radiotracer uptake was within the normal range (1.1%). Follow-up of this patient reveled that the hypothyroidism was transient at Thyroxine replacement was stopped later in life accordingly.

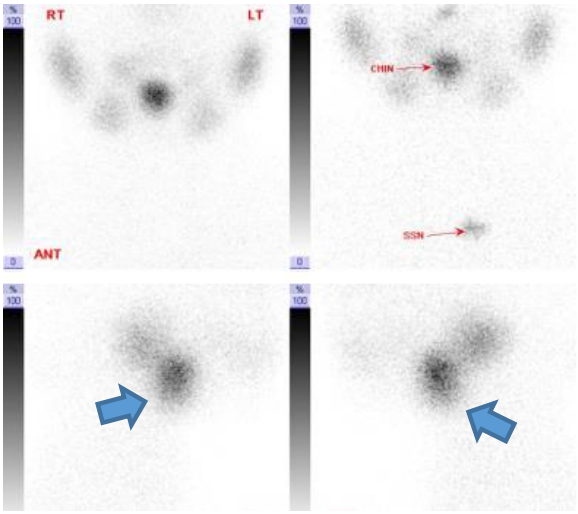


**Figure 2:** Tc-99m pertechnetate Thyroid scintigraphy in a 3 years old male diagnosed with congenital hypothyroidism at birth (top two images are anterior view and the bottom images are left and right lateral views). The study revealed absent radiotracer uptake in the normal thyroid bed and focal radiotracer uptake noted at the base of the tongue (blue arrows), in keeping with sublingual ectopic thyroid. This patient will require lifelong T4 replacement therapy.

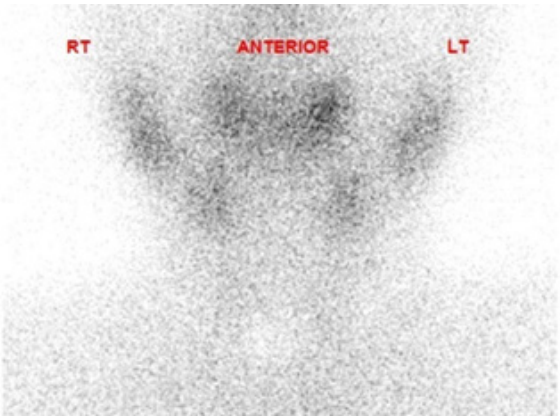


**Figure 3:** Tc-99m pertechnetate Thyroid scintigraphy in a 3 years old female diagnosed with congenital hypothyroidism at birth. The study revealed absent radiotracer uptake in the normal thyroid bed in keeping with thyroid gland agenesis. Finding was also confirmed by absent thyroid tissue on neck Ultrasound (Images not included).

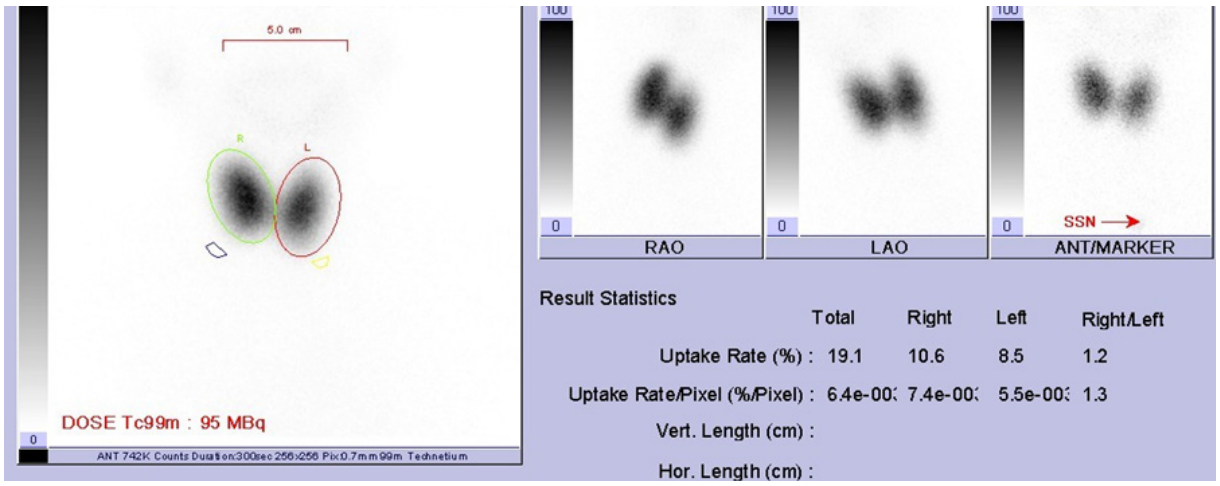


**Figure 4:** Tc-99m pertechnetate Thyroid scintigraphy in a newborn female with elevated cord blood and serum TSH level. The study revealed significantly increased radiotracer uptake in both thyroid lobes in keeping with dyshormonogenesis.

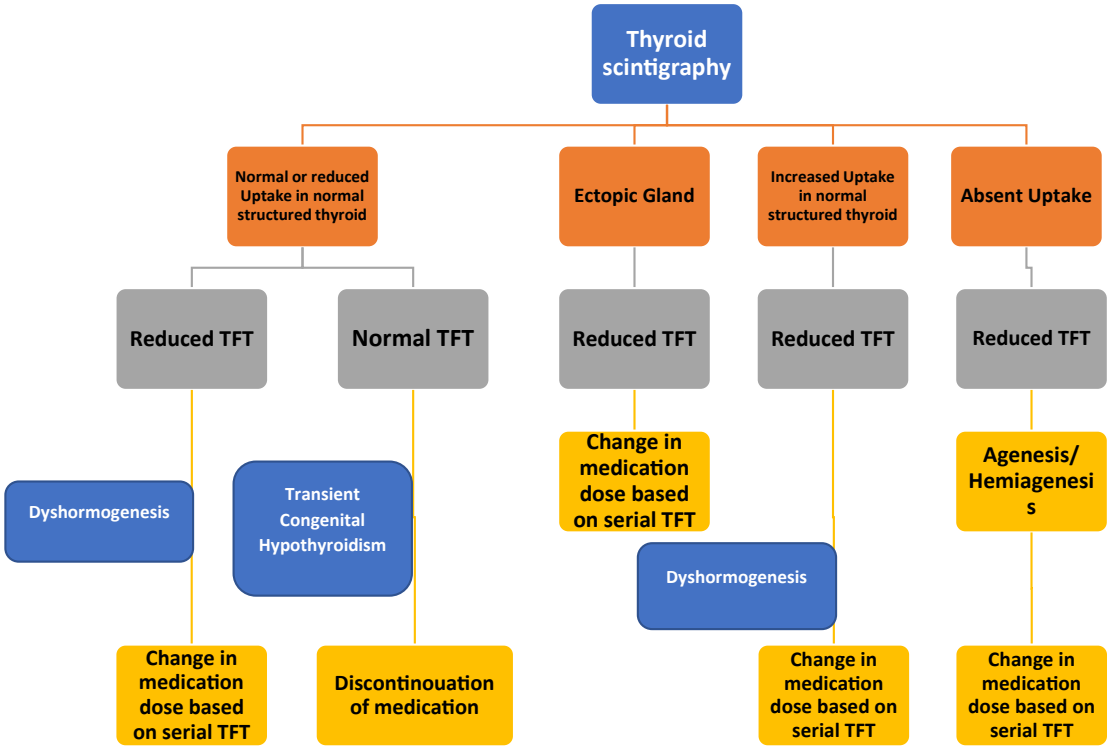


**Diagram 1:** Flow chart of management change based of Thyroid scintigraphy, Thyroid US and serial Thyroid Function test.

mutations and thus have no increased risk of recurrence in future pregnancies, a small percentage of patients have a hereditary defect in thyroid hormone biosynthesis (dyshormonogenesis) as the underlying cause of congenital hypothyroidism. However, in the first epidemiological study conducted in Oman it was found that dyshormonogenesis has a high prevalence in Omani population compared to other nations, probably due to the high rate of consanguineous marriage. This was also evident in our cohort, in which dyshormonogenesis was the cause of congenital hypothyroid in 29.7% (30/101) of patients [16]. Dyshormonogenesis may be suspected in infants with congenital hypothyroidism when an increased percentage of Technetium -99m pertechnetate uptake (normal 0.4 – 4%) is seen on their scans. All of inborn errors of thyroid hormone biosynthesis are autosomal recessive and thus carry a 25% risk of recurrence in future pregnancies [17]. In addition, dyshormonogenesis which may be familial may occasionally be associated with hearing disorders, hence genetic counseling is highly indicated [3].

Therefore, thyroid scintigraphy is an integral part for optimal management of congenital hypothyroidism [18,19]. It provides early distinction between transient and permanent hypothyroidism; therefore, parents can then be counselled on certainty of lifelong therapy [20]. In our department we use Technetium -99m Pertechnetate for thyroid scintigraphy assessing both location of thyroid tissue (ectopic at the thyroid bed or ectopic at the base of the tongue) and uptake percentage of Technicum -99m Pertechnetate concentrated in Thyroid tissues (normal range of 0.4% - 4% is used in our department). Another option for performing thyroid scintigraphy is by using Iodine-123 ($^{123}$I) [12,13]. However, most nuclear medicine departments, including our department, are reluctant to use it, partly because it is more expensive than Technetium-99m Pertechnetate and partly due to the cumbersome channels required to order it in, whereas Technetium-99m Pertechnetate is more readily available.

When the thyroid gland is absent or ectopic (anatomical defect or thyroid dysgenesis), parents are counselled for their children's need of lifetime thyroid hormone therapy. If, on the other hand, the thyroid gland is present in normal position but possibly nonfunctioning, the child may not need permanent treatment if their condition is transient as demonstrated by controlled withdrawal of thyroxine at an older age. Parents rightly expect this maximal clinical and laboratory information at the immediate newborn period. Hence, screening programs for congenital hypothyroidism (CH) have virtually eradicated mental retardation and impaired somatic growth caused by thyroid hormone deficiency. This has been achieved by early diagnosis and treatment with L-thyroxine [21]. In the most recent local demographic study on congenital hypothyroid, the rate of developmental delay was reported to be 11% [16]. However, in our cohort there were 18.9% (19/101) patients with developmental delay. The differences between the two studies results can be attributed to evaluating patients referred from all secondary and tertiary care centers in the country in Al Jafari et al. study, whereas our demographic study was done on patients seen in one institute only, making their results more representative of the Omani population.

It is long claimed that maximal diagnostic data, including results of scintigraphy, offer parents and clinicians an optimal opportunity for the most effective counseling and lifetime management of congenital hypothyroidism, beginning at birth [17]. In our cohort, there was a change in management in slightly over one third of patients 39.6%, based on the thyroid scintigraphy's outcome, thyroid ultrasound and serial thyroid function test results. The main change was either to reduce or stop thyroid hormone mainly due to transient congenital hypothyroidism or increase thyroid hormone dose which was observed mostly in patients with thyroid ectopia. The true prevalence of transient congenital hypothyroidism in this cohort could not be accurately estimated, because electronical tracking and therefore identification of all cases with discontinued thyroid treatment later during their management course was not possible. This was due to referring patients to other regional institutions for long-term follow-up and management. 59.4% (60/101) of our patients only had complete electronical data including post thyroid scan follow-ups.

The American Academy of Pediatrics Task Force Report on congenital hypothyroidism described newborn thyroid imaging as optional and thus encouraged only limited use of the procedure due to the uprising role of genetic studies where feasible [4]. The concern of delaying thyroxine therapy to newborns diagnosed with congenital hypothyroidism on screening programs and the fear of radiation exposure led to hesitancy to recommend scintigraphic evaluation for children with congenital hypothyroidism; especially those living a far distance away from nuclear medicine facilities. We believe that neither concern is warranted. In fact, some clinicians do not advocate the use of imaging for anatomic diagnosis of congenital hypothyroidism because they believe that the results of the thyroid scintigraphy whether the thyroid gland is present or absent does not alter management of congenital hypothyroidism. The worry on radiation exposed to infants is irrational since the whole body absorbed radiation dose for scintigraphy is equivalent to the amount of radiation received during a round-trip (10-hour) transcontinental flight on a commercial airline or during one month living at sea level (normal background radiation: 10 rem) [15]. In addition, thyroid scintigraphy using Technetium 99m has been used for decades with no evidence of increased risk of Thyroid cancer [22].

## Conclusion

Thyroid scintigraphy with Technetium 99m pertechnetate is an integral investigation in any screening program for congenital hypothyroidism. It can differentiate between various causes of CH and thus assist in their proper management. Although, thyroid scintigraphy is an essential investigation in our national guidelines, most of the biochemically diagnosed CH had their scintigraphy done after the age of 3 years and some up to 12 years of age. This necessitates to advocate for more awareness programs for our primary health care practitioners and secondary care pediatricians about the national screening program and early utilization of thyroid scintigraphy to achieve optimal treatment plans.

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