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CLINICAL STUDY

Pitfalls in the diagnosis of thyroid dysgenesis by thyroid ultrasonography and scintigraphy

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Abstract

Objectives: We aimed to investigate the reliability of thyroid ultrasonography (US) and scintigraphy in determining the type of thyroid dysgenesis (TD).

Methods: The study included 82 children (8.0±5.6 years) with a diagnosis of TD by thyroid scintigraphy with ^{99m}Tc and/or US. The patients were re-evaluated 6.0±5.1 years after the diagnosis. Thyroid US was performed in all cases, regardless of the previous US imaging. Scintigraphy images performed at the time of diagnoses ($n=60$) were re-evaluated during the study. Those who had no scintigraphy at the time of diagnosis ($n=22$) or had discordant findings with US ($n=6$) underwent a new scintigraphy.

Results: Scintigraphies revealed no uptake in 37, ectopia in 35, and hypoplasia in 10 cases. The sensitivity vs specificity for US to detect athyreosis, ectopia, and hypoplasia at the time of initial diagnoses was 90.5 vs 47.8, 10 vs 100, and 100 vs 80.4% respectively. The sensitivity vs specificity for scintigraphy at the time of initial diagnoses was 96.2 vs 100, 92 vs 97.1, and 100 vs 96%, respectively, for each diagnosis. Re-scintigraphy at the time of the study led to a change in the initial diagnosis of 3/6 cases. Repeated US showed disappearance of previously reported hypoplastic thyroid tissues in eight patients.

Conclusion: US alone could not differentiate ectopia and athyreosis, whereas scintigraphy alone is also prone to mistakes in newborns and young ages. Dual thyroid imaging is important for precise structural definition of TD.

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Introduction

Thyroid dysgenesis (TD) accounts for 85% of permanent congenital hypothyroidism and, is seen in 1:5000 live births (1). TD is manifested as ectopic thyroid tissue, athyreosis, hypoplasia, and hemiagenesis of the thyroid gland (1). Thyroid scintigraphy by ^{123}I or ^{99m}Tc pertechnetate is the imaging tool in diagnostic evaluation of a patient with congenital primary hypothyroidism. It shows the isotope uptake, position and rough anatomic structure of the thyroid gland, although it is less helpful in the assessment of thyroid size and morphology. Furthermore, isotope scanning is not readily available in all units, and the results might be obscured by prior exposure to iodine-containing agents, or thyroid hormone treatment, depending on the isotope used. Thyroid ultrasonography (US) is increasingly being used for the imaging of thyroid gland in infants with congenital hypothyroidism because of being totally radiation-free and ease of availability. US is valid in assessment of eutopic thyroid tissue in cases with congenital hypothyroidism, although considerable experience is required to differentiate between dysplastic non-thyroidal tissue and thyroid hypoplasia. However, it's not very accurate at differentiating ectopia or athyreosis in the absence of thyroid gland at normal position (2, 3).

In this study, we aimed to determine the sensitivity and specificity of thyroid US and scintigraphy in diagnosis of athyreosis, thyroid ectopia, and thyroid hypoplasia and their drawbacks in the diagnosis of TD.

Materials and methods

This study was performed in the Pediatric Endocrinology Clinics of three main tertiary care hospitals in Istanbul. The study was conducted according to the Declaration of Helsinki after obtaining approval of the ethics committee of the Marmara University Medical School. Written informed consent was obtained from

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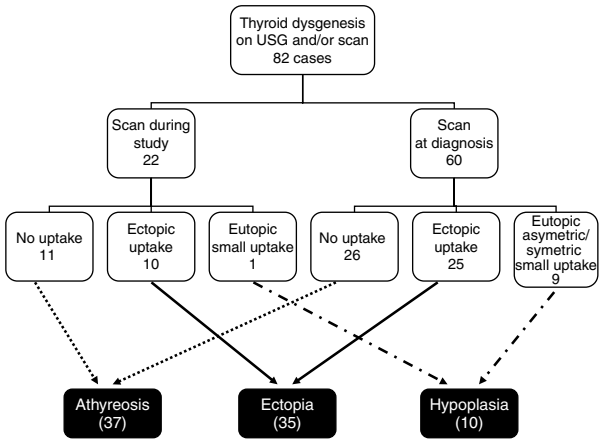

Figure 1 The schematization of the study protocol that shows grouping of the patients according to the final diagnosis, primarily based on the thyroid scan.

the parents of each child and from the patient if older than 16 years of age.

Congenital primary hypothyroidism was diagnosed either by neonatal screening or testing the symptomatic patients who had suggestive symptoms of hypothyroidism in the presence of high TSH, low tetra-iodothyronine (T_4), and free-T_4. Among the patients with congenital hypothyroidism, those with normal or enlarged ectopic thyroid gland on US/or thyroid scintigraphy were excluded from this study to eliminate the patient with dyshormonogenesis from the study. Thus, we aimed to include only cases with TD. Ninety-five children who were diagnosed with TD (agenesis, ectopia, or hypoplasia) by initial thyroid US and/or thyroid scintigraphy were invited to participate in the study. Of these 95 patients, 13 were excluded from the final analyses, either because they were not recruited to scintigraphy ($n=9$) or their diagnoses was changed to dyshormonogenesis ($n=4$). Eighty-two patients with definitive diagnoses of TD were included in the final analyses (Fig. 1).

For this study, we re-evaluated these patients 6.0 $\pm$5.1 years (0–18.9 years) after the initial diagnosis. The thyroid US was performed in all cases by a single experienced radiologist, who was blind to the initial diagnosis (I A), in which, 37 did not have any previous US evaluation. All thyroid scintigraphy images performed at the time of initial diagnosis ($n=60$) were re-evaluated at the time of the study by a single nuclear medicine specialist (F D). Those who did not have scintigraphy at the time of the initial diagnosis and were older than 3 years of age at the time of the study ($n=22$) underwent thyroid scintigraphy 4 weeks after cessation of L-thyroxin. In addition, six patients who had scintigraphy at the time of initial diagnosis, but unclear scintigraphy findings in re-evaluation of the original scintigraphy, or had discordant scintigraphy findings from the second US, also underwent new thyroid scintigraphy.

A final diagnosis was made for each patient after re-evaluation and completion of both imaging methods. The sensitivity and specificity of the US and scintigraphy at the time of the initial diagnosis for diagnosis of different types of TD were calculated based on the final diagnosis.

Thyroid US was performed by gray-scale US with a 7 MHz linear probe (GE Medical System MR Logic 700, Milwaukee, WI, USA) and pre-warmed gel. The subjects were examined in the supine position with hyperextended neck. The sonogram was evaluated for the following features; presence or absence of thyroid gland and isthmus at normal location, each lateral lobe volume (length$\times$breadth$\times$depth$\times$0.5) calculated by measuring three dimensions, anterior cervical area through suprasternal area for ectopic thyroid tissue and echogenicity of the gland. Thyroid volume (sum of two lateral lobes) of each subject was compared with normative data obtained from reference population living in Istanbul to avoid misinterpretation related to regional iodine related changes in the thyroid volume (4).

^{99m}Tc scintigraphy was performed by gamma camera (GE Medical System XCT) equipped with a pinhole (aperture 5 mm in diameter) and/or low-energy high-resolution parallel-hole collimators. Anterior and lateral images were obtained in supine position with the neck extended and supported by a pillow placed under the shoulders. After i.v. injection of 1–2 mCi of $^{99m}TcO_4$ images (256$\times$256 matrix with 1.33 or 2 zoom factor) were acquired for 100 000 and 500 000 counts for pinhole and parallel-hole collimators respectively. The presence, absence, size, and location of areas of $^{99m}TcO_4$ uptake were recorded.

TSH, T_4, and free-T_4 levels were analyzed with E170 Modular Analytics Immunoassay Analyzers by the Electrochemiluminescence Immunoassay method. Thyroglobulin levels were analyzed by the same method in Elecsys 2010 Immunoassay Analyzers.

Results

Eighty-two (31 males and 51 females) cases with TD were included in the final analysis. The mean age of the patients was 8.1$\pm$5.5 years (0.1–23.8 years). Demographic data of the patients are presented in Table 1.

Athyreosis was the final diagnosis in 37 (13 males and 24 females) of the patients (45%). The sensitivity vs specificity was 90.5 vs 47.8 and 96.2 vs 100% for US and scintigraphy to detect athyreosis at the time of initial diagnosis respectively (Table 2).

In all cases with athyreosis, US showed hyperechogenic structures (Fig. 2, panel B) on both sides of the trachea, replacing the normal thyroid tissue. In addition, ten subjects in this group showed cystic

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Table 1 Demographic and laboratory data of the patients with thyroid dysgenesis (TD) according to type of TD. Data are presented as median (range) or as indicated.

	Athyreosis	Ectopia	Hypoplasia
n	37	35	10
Gender (male/female)	13/24	11/24	7/3
Age at diagnosis (years)	0.25 (0–10.5)	0.75 (0–15.5)	0.87 (0.02–10.2)
Current age (years)	9.5 (0.25–19)	8.5 (0.1–23.8)	4.5 (0.3–11.5)
Thyroglobulin (ng/ml;/*n*)	4.0 (0.1–55.6)/16	34.5 (1.5–262.3)/18	35.8 (5.4–61)/4
TSH (μIU/ml)[a]	153 (8–1188.8)	130 (24.8–597.5)	7.3 (6.9–527.6)
Cystic structures on US (*n*)	10	12	1

US, ultrasonography.
[a]TSH levels reported here are simultaneous levels with thyroglobulin measurements, thus a few of them were taken after treatment was initiated.

structures: four on the left, five on the right, and one on both sides of the trachea.

Ectopic thyroid gland was detected in 35 (11 males and 24 females) of the 87 cases (43%) on thyroid scintigraphies. Three and six of the 35 patients had submental and lingual thyroid gland, respectively, and the remaining 26 patients had sublingual uptake on scintigraphy. The sensitivity vs specificity of US to diagnose thyroid ectopia was 10 vs 100% at the time of initial diagnosis. Moreover, sensitivity vs specificity of scintigraphy at the time of diagnosis was 92 vs 97.1% (Table 2).

Similar to the patients with thyroid agenesis, all patients with thyroid ectopia also had hyperechogenic structures on both sides of the trachea on ultrasonographic examination. Of these, 12 subjects showed additional cystic structures: six on the left, five on the right, and one on both sides of the trachea (Fig. 2, panel C). One patient in this group had two separate ectopic uptakes in the neck region on scintigraphy consistent with double ectopia (Fig. 3). Subjects diagnosed with hypoplasia by thyroid scintigraphy ($n=10$, 12%) (7 males and 3 females) were shown to have hypoplastic thyroid gland by US when thyroid volume was compared with the age-matched normative values (4). No hyperechogenic structures were detected in this group, however, one patient with hypoplasia showed a cystic structure with diameters of 3.2 and 5.2 mm on US in the left thyroid lobe. The sensitivity and specificity of thyroid USG at the time of the diagnosis were 100 and 80.4% for hypoplasia respectively. At the time of the diagnosis, the sensitivity and specificity of scintigraphy to detect thyroid hypoplasia were 100 and 96% respectively (Table 2).

The patients presented before age of 3 months constituted 51.2% of the study population. Etiologic distribution of the cases in this group was as follows: athyreosis 51%, ectopia 37%, and hypoplasia 12%. For this age group, sensitivity vs specificity of US was 84.6% (95% confidence interval (CI): 53.7–97.3%) vs 36.3% (95% CI: 53.7–97.3%) for athyreosis, 0% (95% CI: 0–37.1%) vs 100% (95% CI: 74.7–100%) for ectopia, and 100% (95% CI: 19.8–100%) vs 81.8% (95% CI: 59–94%) for hypoplasia at the time of diagnosis. The sensitivity and specificity of scintigraphy to detect athyreosis, ectopia, and hypoplasia were all 100% except the sensitivity of ectopia, which was 91.6% (95% CI: 59.7–99.6%) and the specificity of hypoplasia, which was 96% (95% CI: 77.7–99.8%).

In three out of six patients in whom thyroid scintigraphy was repeated at the time of the study, the final diagnosis was changed; one patient with ectopia changed to athyreosis and two patients with thyroid hemiagenesis changed to ectopia.

US findings at the time of the diagnosis and at the time of the study were also discordant in 8 out of 82 patients. In six of them with scintigraphic diagnoses of ectopia, US at diagnosis were reported as hypoplastic thyroid tissue in normal location whereas US at the time of the study showed no thyroid tissue in the normal location. In one patient, US at diagnosis was reported as hemiagenesis while US at the time of the study showed no thyroid tissue in the normal location. Similarly, in one patient with scintigraphic diagnosis of athyreosis,

Table 2 US and scintigraphy findings at diagnosis and at the time of the study and the sensitivity and specificity (presented as % (95% CI)) of each imaging method alone at diagnosis based on final diagnoses at the time of the study.

	US at diagnosis			Scan at diagnosis		
	n[a]	Sensitivity	Specificity	*n*[a]	Sensitivity	Specificity
Athyreosis ($n=37$)	21	90.5 (68.1–98.3)	47.8 (27.6–68.9)	26	96.2 (78.4–99.7)	100 (87.3–100)
Ectopia ($n=35$)	20	10 (1.7–33.1)	100 (82.8–100)	25	92 (72.5–98.6)	97.1 (83.4–99.8)
Hypoplasia ($n=10$)	3	100 (31–100)	80.4 (64.6–90.6)	9	100 (62.9–100)	96 (85.4–99.3)

[a]Indicates number of patients.

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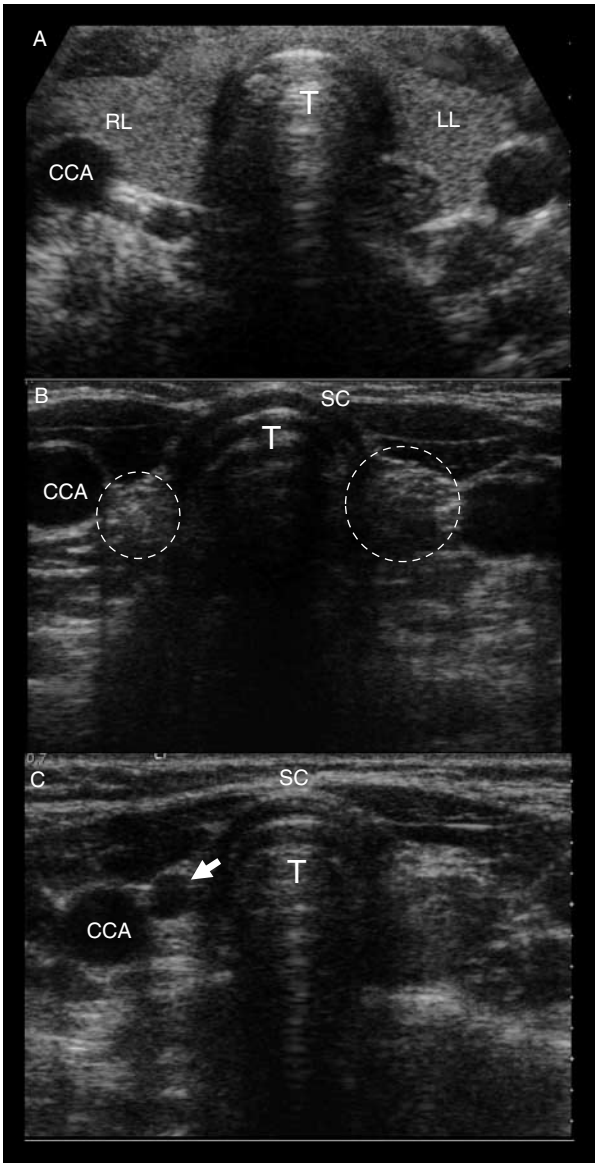

Figure 2 The transverse section of thyroid area at ultrasonography showing normal thyroid gland as right (RL) and left lobes (LL) at panel A, hyperechoic structures compared with normal thyroid tissue on both sides of the trachea (shown by circle) at panel B, and cystic change (shown by arrow) at panel C in the empty thyroid area. T, trachea; CCA, common carotid artery; RL, right lobe of thyroid gland; LL, left lobe of thyroid gland; SC, subcutaneous tissue.

US at the time of the study was reported as thyroid hypoplasia whereas US at the time of the study did not reveal any thyroid tissue.

Discussion

In evaluation of a patient with congenital hypothyroidism, US is helpful to demonstrate eutopic thyroid tissue. When thyroid tissue is not seen on a normal location by US, thyroid scintigraphy is required to understand whether the patient have athyreosis or ectopia. In this study, US detected precisely 37 patients with thyroid agenesis by reporting no detectable thyroid tissue. However, in patients with ectopia, US was able to detect only 2/20 at the initial diagnosis and 3/35 patients at the time of the study correctly. Thus, ~90% of the patients with thyroid ectopia would have been misdiagnosed, if US was the only imaging method used. Thus, the main weakness of US in the evaluation of congenital hypothyroidism is the low detection rate for thyroid ectopia. The ability of thyroid US to detect ectopia is quite variable ranging from 0 to 21% in various studies (5–8). Higher detection rates are reported in studies based on color Doppler US (9, 10). In the study by Tamam *et al.* (9) 20/32 ectopic thyroid were detected by color Doppler US while none was detected by gray-scale US.

Hypoplasia of the thyroid gland was detected in 12% of the cases in this study that was reported to be ranging from 5 to 26% (11–13) in different series. However, hypoplasia as a type of TD was evaluated only in a few studies. We report here a lower ratio (10/87) of hypoplasia compared with another study by Perry *et al.* (13) who reported a ratio of 8/40. It is difficult to diagnose thyroid hypoplasia in newborns and infants with congenital hypothyroidism for several reasons. First, thyroid scintigraphy with ^{99m}Tc is not sensitive enough to interpret thyroid volumes. In addition, the neck of a young infant is short which might lead to the faulty localization of the thyroid tissue. On the other hand, the main difficulty in diagnosing hypoplasia by US is the paucity of normative data for thyroid volumes in newborn babies. Although, some studies reported

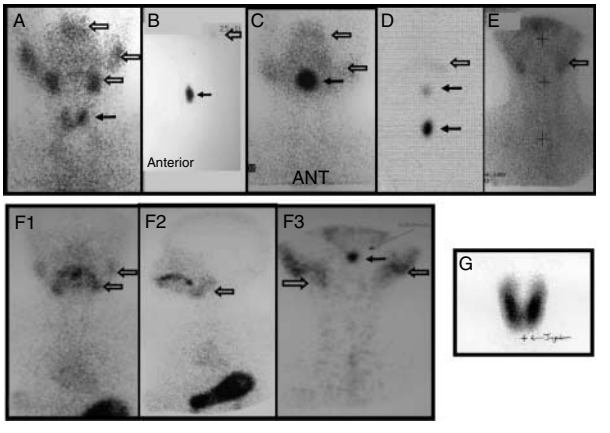

Figure 3 Thyroid scan pictures showing different types of thyroid dysgenesis. At upper panel hypoplasia (A), hemiagenesis (B), ectopia (C), double ectopia (D), and athyreosis (E) compared with normal thyroid (G) shown at lower panel. Panel F showing scintigraphy performed at the time of diagnosis (F1 and F2) reported as hemiagenesis while repeated scintigraphy at the time of the study (at 12 years age) showed ectopia (F3). Radiopharmaceutical uptake by thyroid tissue is shown by black arrows and salivary glands by empty arrows.

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age-adjusted −2S.D. cut-offs for thyroid gland volume in newborns and children, these data show great variability, indicating the necessity of a population-specific data (4, 14–18). Furthermore, these cut-offs are rarely used and interpreted in reports by radiologists since they usually report presence or absence of ectopic thyroid tissue, and give the dimensions of the gland.

In thyroid scintigraphy, the overlapping images of salivary gland and ectopic thyroid tissue are another source of error in young ages. In our cohort, two initial diagnoses of hemiagenesis with scintigraphy later changed to ectopia after repeating scintigraphy (Fig. 3). In addition, one initial diagnosis of ectopic thyroid changed to athyreosis after repeating scintigraphy due to misinterpretation of uptake localizations and mixing with salivary gland images in the initial scintigraphy. These results suggest that scintigraphy performed at later ages is more reliable than those performed at newborn period. Furthermore, scintigraphy with ^{123}I is superior to ^{99m}Tc in detection rate of functional tissues and no significant oral accumulation and, the ectopic thyroid tissue is detected more in scintigraphy with ^{123}I (63 vs 52%) (2). Thus, the errors related to scintigraphy in our study might be related to the use of ^{99m}Tc. Furthermore, we reported a similar ratio of ectopia and athyreosis in our cohort; however, the real ectopia ratio could be higher than reported here because of the ^{99m}Tc we used for the scintigraphy.

Another interesting observation was that 8/82 patients with ultrasonographies performed at the time of the study showed hypoplastic thyroid tissue/hemiagenesis while US at the time of the diagnosis showed no thyroid tissue in the normal location; but, hyperechogenic non-functional tissues, instead. Although these tissues can be recognized by their hyperechogeneity, small size, poor vascularity, and anechoic/hypoechoic cystic features in the empty thyroid area, it is easily described as *in situ* thyroid tissue (hypoplastic or dysplastic) (7, 19–21). The reason of discordant US finding at the time of diagnosis is most probably related to misinterpretation of these hyperechogenic tissues as hypoplasia in our study. The hyperechogenic structures at both sides of the trachea that were detected by US in the empty thyroid area, in cases of either athyreosis or ectopia, are suggested to represent the remnants of ultimobranchial bodies.

In addition to hyperechogenic structures, US revealed cystic structures in the empty thyroid area or within the thyroid tissue in 32% of our subjects with TD (10 in the athyreosis, 12 in the ectopia, and 1 in the hypoplasia groups). In other studies, cystic structures are detected by 68% in a group of patients with ectopia and athyreosis in the childhood period and by 15% in newborn period (7, 19–21). It is notable that despite a wide age range at the time of repeated US in our patients, almost all patients with cystic structures in this study were over 2 years, which suggests that either cystic structures are emerging or becoming visible as the patient gets older. Cysts in the empty thyroid area either in neonatal or childhood period are assumed to be the result of persisting ultimobranchial bodies or thyroglossal duct during the embryogenesis, and there is no evidence that the cysts are functional (7, 19–21).

In conclusion, evaluation of TD by US alone could not differentiate ectopia and athyreosis, whereas thyroid scintigraphy alone is also prone to errors especially in the neonatal period, and does not demonstrate non-functioning thyroid remnants.

Dual imaging with US and scintigraphy allows precise definition of the thyroid phenotype that is important for research aiming to understand thyroid development and possible molecular defects leading to TD in the era of advanced molecular research.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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