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 ⁹⁹mTc 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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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 (T₄), and free-T₄. Among the patients with congenital hypothyroidism, those with normal or enlarged ectopic thyroid gland on US/or thyroid scintigraphy were excluded from this 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 ± 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×breath×depth×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).

99mTc 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 99mTcO₄⁻ images (256×256 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 99mTcO₄ uptake were recorded.

TSH, T₄, and free-T₄ 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 ± 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
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 96% respectively (Table 2).

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,
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
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/hemialgenesis 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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