

Original Article**The role of ultrasonography in primary congenital hypothyroidism**

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Abstract

BACKGROUND: The aim of this study was to compare the usefulness of ultrasonography and scintigraphy in diagnosing the etiology of primary congenital hypothyroidism (CH).

METHODS: The newborns that were examined by both thyroid scintigraphy and ultrasonography during CH screening program in Isfahan were included in this study. The ultrasonographic findings were compared with the scintigraphic findings and the sensitivity and specificity of the ultrasonography was determined.

RESULTS: During this study, 102 CH newborns were studied. According to the ultrasonographic results, 61.8%, 26.5%, 2.9% and 8.8% of them had normal thyroid gland, agenesis, ectopia and hypoplasia, respectively, and according to scintigraphic results, 55.9%, 35.3% and 8.8% of them had normal thyroid gland, agenesis and ectopia, respectively. Ultrasound detected sensitivity, specificity, positive predictive value, negative predictive value, and positive and negative likelihood ratio were 77%, 92%, 89%, 84%, 9.6 and 0.25, respectively. The sensitivity and specificity of ultrasonography compared with thyroid scintigraphy in diagnosis of thyroid gland ectopia was 33% and 100%, respectively.

CONCLUSIONS: Though thyroid ultrasonography failed to diagnose 67% of ectopic cases and nonfunctioning thyroid gland, it had the ability to determine the anatomy of thyroid gland. So, considering some limitations of scintigraphy, we concluded that ultrasonography is a relatively appropriate imaging tool for diagnosing CH etiologies, especially in the initial phase of CH screening.

KEYWORDS: Congenital Hypothyroidism, Etiology, Iran, Radioisotope Scanning, Ultrasonography.

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Congenital Hypothyroidism (CH) is the most common endocrine disorder of the neonates which is seen in 1 out of 3000-4000 live births; the prevalence is influenced by the race and ethnicity. CH results in severe neurodevelopmental impairment if treatment

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is delayed, therefore most countries implement neonatal screening programs for early detection of CH and performing therapeutic interventions.^{1,2} CH is highly prevalent in Iran too; the overall prevalence in major provinces of Iran is 1:914 in Tehran, 1:1433 in Fars and 1:370 in Isfahan.³⁻⁵

The most common etiology of CH is glandular dysgenesis which contains approximately 85% of the cases. Complete agenesis (35-40%), ectopic (55-60%) and hypoplastic (5%) development of the gland are various forms of dysgenesis. Remaining dys-hormonogenetic cases of CH are associated either with a goiter or a normal-sized thyroid gland.⁶

Although the majority of infants are now diagnosed after detection through newborn screening programs using a primary T4-backup TSH or primary TSH, thyroid imaging is necessary in identification of the etiology.

It is extremely important to determine the etiology of the disease for selecting appropriate treatment strategies and understanding the implications of inheritance and prognosis.^{7,8} Thyroid scintigraphy, using ^{99m}Tc or ¹²³I, is the most accurate diagnostic test to detect thyroid dysgenesis or one of the inborn errors of T4 synthesis. While thyroid scintigraphy is the method of choice for determination of CH etiology, ultrasonography as a non-invasive method is also paid attention into some extent for the anatomical evaluation of the thyroid gland.⁹ Thyroid ultrasonography may miss some cases of ectopic glands, so scintigraphy is considered to be more precise in the detection of dysgenetic ectopic thyroid tissue and also an anatomically normal but non-functional gland than ultrasonography.¹⁰⁻¹³

Administration of exogenous thyroxin inhibits TSH secretion and confounds the uptake of radionuclide scanning agents, so scintigraphy must be done before or within the first week of starting treatment. That's why it is not routinely used in neonates with CH diagnosed during CH screening. Scintigraphy is not applicable in sick and preterm infants, also.⁹ Considering all the mentioned factors in addition

to high cost of the scintigraphy lead the practitioners to think about other options like ultrasonography. There are controversial reports about using ultrasonography for diagnosis and determination of CH etiology.¹²⁻¹⁴ Some of them confirmed whereas others denied or recommended to be used in combination with scintigraphy.¹²⁻¹⁴

High rate of CH in our community has led us to determine an appropriate imaging tool that would be more accessible for these patients and result in better outcome of the disease.¹⁵ So, considering the limitations of thyroid scintigraphy and also the value of ultrasonography in assessment of thyroid gland morphology, we carried out the current study to determine the usefulness of this imaging technique in diagnosis of the etiology of primary CH comparing with the gold standard imaging method of scintigraphy, in the CH screening program of Isfahan.

Methods

In this descriptive study, patients diagnosed with CH during CH screening program in Isfahan and referred to Isfahan Endocrine and Metabolism Research Center for treatment and follow up were selected.

CH screening program initiated in 2002 and continued till 2005, when nationwide CH screening program was implemented.

Newborns with abnormal screening results were re-examined and those with abnormal T4 and TSH levels on their second measurement (TSH>10 mIU/l and T4<6.5 µg/dl) were diagnosed as CH patient and received treatment and regular follow up. Hypothyroid neonates underwent treatment at a dose of 10-15 µg/kg/day as soon as the diagnosis was confirmed, with the monitoring of TSH and T4 during follow-up.

The etiology of CH was determined by thyroid scan and/or ultrasound before treatment in neonatal period or at age 3 years after confirming the permanency of CH. Thyroid scan was performed before treatment initiation, otherwise it was done at age 3 years. But, ultrasonography has no time limitation and

could be performed at any time during follow up.¹⁶

The protocol was approved by the Institutional Review Board and Medical Ethics Committee of Isfahan University of Medical Sciences. Written consent was obtained from the parents of CH patients.

In order to compare ultrasonography and thyroid scintigraphy for etiologic diagnosis of CH, newborns that were examined by both thyroid scintigraphy and ultrasonography were included in this study.

Thyroid scintigraphy was performed before or within the first 4 days of treatment initiation. The infants were fed just before thyroid scintigraphy to keep them quiet. Thyroid scintigraphy was performed using a gamma camera equipped with a pinhole collimator (Stintrone, Germany), 20 minutes after intravenous injection of 0.5-1 mci Tc99.

Thyroid ultrasonography of the entire neck was performed by two radiologists in supine position, with the neck hyperextended using HONDA (Japan) ultrasonographic device, with a HLS-475M, 7.5 MHZ linear transducer. The sonogram was evaluated for the following features: 1. absence or presence of the thyroid gland in usual anatomical location, 2. absence or presence of the thyroid lobes and isthmus and 3. presence of thyroid in ectopic localization. Agenesis is characterized by a complete absence of thyroid tissue. Thyroid ectopia was defined as thyroid tissue localization other than in the lower part of the neck. The anterior cervical area was systematically studied for the presence of thyroglossal duct remnants from the foramen caecum to the normal anatomic position of the thyroid gland and even lower,

above the sternal manubrium. Based on the ultrasonographic and scintigraphic studies, patients were classified into two main categories: 1. normal gland in usual location and 2. abnormal results which contains agenesis and ectopia in the case of scintigraphy and agenesis, ectopia and hypoplasia in the case of ultrasonography.¹⁷

Both the nuclear medicine specialist and sonographer were blind to the etiology of CH.

Final diagnosis was performed by a pediatric endocrinologist, according to the clinical, biochemical and radiology data in each CH patient.¹⁵

The ultrasonographic findings were compared with the scintigraphic findings and the sensitivity and specificity of the ultrasonography were determined. In addition, likelihood ratio (LR) was calculated in order to estimate the probability of the disease diagnosis by ultrasonography. Data were analyzed using SPSS 13. p - value < 0.05 was considered statistically significant.

Results

During this study, 102 CH patients who were diagnosed, treated and followed up during CH screening program of Isfahan and were examined by both thyroid scintigraphy and ultrasonography were studied. From studied patients 56 (54.9%) were male and 6 (5.9%) were premature (3 males). The age of initiating treatment was 17.9 ± 10.9 days (3-62 days). The scintigraphic and ultrasonographic findings of studied cases according to normal and abnormal thyroid glands are presented in Table 1. 63 patients (37 male) had normal gland in usual location according to ultrasonographic

Table 1. Scintigraphic and ultrasonographic findings of studied population regarding to normal and abnormal thyroid gland

	Normal ultrasonography	Abnormal ultrasonography
Normal scintigraphy	53 ¹	4 ³
Abnormal scintigraphy	10 ²	35 ⁴

- 1 True negative
- 2 False negative
- 3 False positive
- 4 True positive

findings and 39 (19 male) had abnormal ultrasonographic results ($p > 0.05$). 57 patients (33 male) had normal gland in usual location according to scintigraphic findings and 45 (23 male) had abnormal scintigraphic results ($p > 0.05$).

Ultrasound sensitivity, specificity, positive predictive value, negative predictive value, LR+ and LR- were 77%, 92%, 89%, 84%, 9.6 and 0.25, respectively. The sensitivity and specificity of ultrasonography compared with thyroid scintigraphy in diagnosis of thyroid gland ectopia was 33% and 100%, respectively, according to the results presented in Table 2.

The ectopic thyroid glands (6 cases) which could not be diagnosed by ultrasonography included agenesis in 5 cases and hypoplasia in 1 case. The ultrasonographic and scintigraphic results and the final diagnoses are presented in Table 3. There were 10 cases of disagreement between ultrasonography and scintigraphy, in which a normal thyroid gland was identified by ultrasonography in the usual anatomical location whereas scintigraphy reported non-functional thyroid gland with no uptake. There was also a case of hypoplasia identified by ultrasonography but scintigraphy reported it as non-functional thyroid gland with no uptake. In 8 cases that were diagnosed with hypoplasia by ultrasonography, 4 reported as agenesis and 4 as normal thyroid gland by scintigraphy. According to the biochemical and clinical results and decision of pediatric endocrinologist, all 8 cases classified as hypoplasia in final diagnosis.

Discussion

In the present study, comparison of the findings of ultrasonography with scintigraphy,

demonstrated that this imaging technique is useful for early diagnosis of different etiologies of CH during screening program. The findings of this study, likewise other studies, showed that ultrasonography could reflect the anatomical status of the thyroid gland.¹⁴

However, ultrasonography had some weaknesses in diagnosing ectopic thyroid gland.¹⁸ In this study, only 33% of ectopic thyroid glands were diagnosed by ultrasonography. In another similar study which was performed among 54 CH patients, only 5 out of 26 cases with ectopic thyroid gland were diagnosed by ultrasonography.¹⁹ In a similar recent study in Korea, discordant cases of CH according to the comparison of findings of ultrasonography and scintigraphy were investigated; in 6/300 patients, ultrasonography was not able to detect the ectopic thyroid gland and its sensitivity in this field was 78%, which was higher than ours. The specificity of ultrasonography in this field was 100%, which was similar to our results.²⁰

Another weakness of this imaging tool is its limited value for the evaluation of thyroid gland function, whereas scintigraphy reflects the functional status of the gland.¹⁴ Therefore, it may identify an anatomically normal but nonfunctional gland.^{11,14} In the current study, 63/102 cases were reported to have normal thyroid gland by ultrasonography and this proportion was 57/102 for scintigraphy, but according to final diagnosis, 53 cases were normal. In 10 cases of agenesis, ultrasonography reported normal gland, which consequently decreased the specificity of ultrasonography to 92 %.

Change et al. reported 42/300 subjects with normal thyroid gland by ultrasonography and

Table 2. The sensitivity and specificity of ultrasonography compared with thyroid scintigraphy in the diagnosis of thyroid gland ectopia

	Not ectopic(scintigraphy)	Ectopic(scintigraphy)
Ectopic(ultrasonography)	0 ³	3 ⁴
Not ectopic(ultrasonography)	97 ¹	6 ²

- 1 True negative
- 2 False negative
- 3 False positive
- 4 True positive

Table 3. Etiology of CH according to the ultrasonographic and scintigraphic findings and the final diagnosis of studied CH patients

Etiology	Ultrasonographic findings	Scintigraphic findings	Final diagnosis
Normal	63(61.8)	57 (55.9%)	(51.9%) 53
Agenesis	27 (26.5%)	36(35.3%)	32 (31.4%)
Ectopia	3 (2.9%)	9 (8.8%)	9 (8.8%)
Hypoplasia	9 (8.8%)	-	8 (7.9%)
Total	102	102	102

this proportion was 55/300 for scintigraphy.²⁰ In the study of De Bruyn et al., in 54 hypothyroid neonates, 4 nonfunctional thyroid glands were reported as having normal thyroid gland by ultrasonography.

These findings could be due to maternal suppressing TSH receptor blocking antibodies, transient elevated thyrotropin, hypopituitarism and unknown causes.^{19,20} So, it seems that mentioned factors should be evaluated in these cases in future studies.

Several studies have investigated the usefulness of ultrasonography in determining different etiologies of CH and they have reported controversial results in this field. Some of them concluded that ultrasonography has limited value in diagnosing the etiologies of the disease. Muir et al. in their comparative study between ultrasonography and scintigraphy among 54 congenitally hypothyroid neonates have reported that none of 13 patients with thyroid ectopia was detected with ultrasonography and 4 cases of agenesis had a normal gland according to ultrasonographic results. Therefore, they concluded that ultrasonography could not be considered as the alternative method to scintigraphy to define the causes of CH.¹²

Other authors confirmed the usefulness of ultrasonography specially for the initial evaluation of CH and they recommended that scintigraphy should be used as a complementary imaging tool where ultrasonography is not capable of identifying accurately the etiology of CH. But, the indication of using scintigraphy was different in the mentioned studies.

Bubutshvili et al. in their study among 66 CH patients, in 2003 in France, have reported that in 12 cases for which no iodine uptake was

demonstrated by scintigraphy, ultrasonography showed normally located thyroid tissue in 2 patients and the sensitivity of ultrasonography in identifying ectopic tissue was 21%. They concluded that ultrasonography may reveal additional findings with regard to those obtained by scintigraphy such as information regarding the anatomy and morphology of the thyroid gland and scintigraphy is required in patients with no visibility of the thyroid gland in its normal location or those with goiter.²¹

Takashima et al. have reported that ultrasonography showed 75% sensitivity for detecting thyroid ectopia. According to their recommendation, scintigraphy is necessary for patients with absent gland in normal location on ultrasonography to confirm ectopia and to differentiate between ectopia and true aplasia. According to their final report, careful ultrasonography of the neck in association with biochemical laboratory data is enough in more than 54% of CH patients and the indication of scintigraphy was similar to that recommended by Bubutshvili et al.¹⁴ Although Kreisner et al. in their study among 89 cases of CH have the same conclusion about the utility of ultrasonography, their recommendation about the indication of scintigraphy assessment was different. They concluded that scintigraphy should be used to discriminate between different types of dysgenesis identified by ultrasonography.¹¹

Recently, Perry et al. determined the strengths and weaknesses of two mentioned imaging techniques in 40 primarily diagnosed CH neonates and they concluded that the scintigraphy had superiority in diagnosing thyroid ectopia whereas ultrasonography had ability to detect tissue that was not visualized on scinti-

graphy and to show abnormalities of thyroid volume and morphology. So, they concluded that combined ultrasound and isotope scanning is more informative in the diagnosis of CH etiology.¹³ Change et al. in their recent similar study in Korea have reported the same conclusion.²⁰

The limitation of the current study was that we did not evaluate inter- and intra-observer CV.

In sum, given mentioned reports and the results of our study, though ultrasonography had failed to diagnose 67% of ectopic cases and nonfunctioning thyroid glands, it had the ability to determine the anatomy of thyroid gland. So, it seems that the combined imaging methods would be more preferable in this field. But, considering our experience during CH screening program which indicated that most parents refused to do scintigraphy because of its limitations and their fear of radiation, our recommendation is to consider further scintigraphic evaluation of ectopic cases failed to be diagnosed by ultrasonography and were misinterpreted as agenesis or hypoplasia of the thyroid gland; because otherwise they will be finally

classified as thyroid dysgenesis and this could explain the low rate of CH due to ectopia in our studied population in contrast to others¹⁶. On the other hand, the superiority of ultrasonography in assessment of gland morphology can introduce it as a relatively appropriate imaging tool for diagnosing CH etiologies especially in the initial phase of CH screening. In cases with normal thyroid gland reported by ultrasonography, in order to determine the etiology of CH (transient or permanent CH with dyshormonogenesis or non-functioning thyroid gland), first we could consider the screening tests of TSH and T4 levels. However, Iranpour et al. in their study in the same population in Isfahan have reported that neonates with thyroid agenesis had significantly higher serum TSH value during screening.²² Thyroid scintigraphy was able to diagnose these cases that both ultrasonographic and biochemical findings were not able to correctly determine the etiology of CH for them. In addition, thyroid scintigraphy should be assessed to discriminate between agenesis and ectopia when CH patients reevaluated at 2-3 years old to determine the permanency of CH.

Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

All authors participated in designing and conducting the study. RB and AH participated in performing radiologic studies. MH and SH drafted and edited the manuscript. All authors read and approved the manuscript.

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