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Sonographic assessment of congenitally hypothyroid children in Iran

Badanie ultrasonograficzne szyi u irańskich dzieci z wrodzoną niedoczynnością tarczycy

Mohsen Hoseini[1], Ali Hekmatnia[1], Mahin Hashemipour[2], Reza Basiratnia[1], Navid Omidifar[2], Afshin Rezazade[1], Razie Koohi[1]

[1]Department of Radiology, Isfahan University of Medical Science, Iran
[2]Endocrine & Metabolism Research Centre, Isfahan University of Medical Science, Iran

Abstract

Introduction: Considering the high prevalence of congenital hypothyroidism (CH) in Isfahan, it seems that it is necessary to investigate the aetiology of the disorder and its related factors. The aim of this study was to determine the aetiology of CH among children in Isfahan province.

Material and methods: In this cross-sectional study, the aetiology of CH and the volume of the thyroid was assessed using neck ultrasonography. The results of thyroid function screening tests were additionally recorded. The correlation between ultrasonographic findings and the level of TSH and as well as T4 was determined.

Results: During this study 385 CH patients aged 0–3 years were studied. According to ultrasonographic findings, in 19.9% of patients the aetiology of CH was dysgenesis (agenesis, ectopy, and hemiagenesis) and 80.1% had normal thyroid. Mean thyroid gland volume in all studied patients was 0.78 ± 0.44 mL. The prevalence of ultrasonographic findings was as follows: normal 80.1%, agenesis 12.7%, hemiagenesis 5.8%, and ectopy 1.4%. There was a significant correlation between thyroid volume and TSH and T4 and as well as between TSH and ultrasonographic findings ($p < 0.05$).

Conclusions: In spite of the limitations of ultrasonography in the field of determining the aetiology of CH, it is an appropriate imaging tool for determining the volume of the thyroid gland in children. Considering that the rate of goitrous gland was low, it seems that iodine deficiency could not be responsible for the high rate of CH in this region. **(Pol J Endocrinol 2010; 61 (6): 665–670)**

Key words: *congenital hypothyroidism, thyroid volume, ultrasonography*

Streszczenie

Wstęp: Z uwagi na częste występowanie w Isfahanie wrodzonej niedoczynności tarczycy (CH, *congenital hypothyroidism*) należy wyjaśnić przyczyny powstania tego zaburzenia i sprzyjające jego rozwojowi czynniki. Celem badania było ustalenie etiologii CH u dzieci zamieszkałych w prowincji Isfahan.

Materiał i metody: W tym przekrojowym badaniu przeprowadzono badanie ultrasonograficzne szyi w celu oceny wielkości tarczycy i ustalenia etiologii niedoczynności tego narządu. W ramach programu badań przesiewowych wykonano testy oceniające czynność tarczycy. Zbadano korelacje między wynikami badań ultrasonograficznych a stężeniami TSH i T4.

Wyniki: Do badania włączono 385 dzieci z CH w wieku 0–3 lat. Badania obrazowe wykazały, że u 19,9% chorych przyczyną CH były zaburzenia rozwoju tarczycy (agenezja, ektopia i hemiagenezja). Średnia objętość gruczołu tarczowego w badanej grupie wynosiła 0,78 ± ± 0,44 ml. Uzyskano następujące wyniki badań ultrasonograficznych: obraz prawidłowy u 80,1% dzieci, agenezja — 12,7%, hemiagenezja — 5,8%, ektopia — 1,4%. Stwierdzono istotną korelację między wielkością tarczycy a stężeniem TSH i T4 oraz między stężeniem TSH a wynikami badań ultrasonograficznych ($p < 0,05$).

Wnioski: Mimo ograniczeń ultrasonografii, jako metody określania etiologii CH, ten rodzaj badań obrazowych jest przydatny do oceny wielkości tarczycy u dzieci. Biorąc pod uwagę rzadkie występowanie wola u dzieci z CH, można przypuszczać, że niedobór jodu nie jest przyczyną wysokiej zachorowalności na tę chorobę w prowincji Isfahan. **(Endokrynol Pol 2010; 61 (6): 665–670)**

Słowa kluczowe: *wrodzona niedoczynność tarczycy, objętość tarczycy, ultrasonografia*

Navid Omidifar MD, General Practitioner. Research Assistant, Endocrine & Metabolism, Research Centre, Isfahan University of Medical Science, Isfahan Endocrine & Metabolism Research Centre, Sedigheh Tahereh Research Centre, Khorram St., Jomhouri Square, Isfahan, Iran, tel.: +98 311 335 99 33, fax: +98 311 337 37 33, e-mail: omidifar@edc.mui.ac.ir

Introduction

Due to its high prevalence, congenital hypothyroidism (CH), being the most common endocrine disorder and preventable cause of mental retardation in neonates, is considered a major health problem in Iran. The condition affects about 1:3000 to 1:4000 infants and may be caused by thyroid dysgenesis or dyshormonogenesis [1, 2].

Thyroid developmental anomalies, which include thyroid agenesis, ectopic thyroid tissue, thyroid hypoplasia, and thyroid hemiagenesis, are responsible for 85% of CH patients. The possible role of genetic factors, autoimmune, or unknown environmental factors has been suggested in the pathogenesis of thyroid dysgenesis [3–5]. In the remaining 15%, CH results from dyshormonogenesis, with a defect in the biochemical mechanisms of thyroid hormone synthesis. This form of CH is transmitted by autosomal recessive mode and numerous causative mutations have been identified [6, 7].

According to the reports on CH screening in Iran, it is detected at a rate of 1:914 live births in Tehran, 1:1433 in Fars, and 1:370 in Isfahan [8–10].

The high rate of CH in our community emphasizes the necessity of determining the aetiology of CH and its related factors, especially due to the high rate of parental consanguinity. Many studies have been performed in this field: some of them have determined the role of genetics factors and others the role of environmental ones [11–13].

Although thyroid scintigraphy is the method of choice for diagnostic confirmation and determination of CH aetiology [14], ultrasonography is considered a non-invasive method for the anatomical evaluation of the thyroid gland and initial evaluation of CH [14]. Scintigraphy has to be performed before or within the first week after treatment initiation, as exogenous thyroxin will interfere with the uptake of radionuclide scanning agents and it has a high cost, so it is not routinely used in newborn infants diagnosed by screening [15].

Considering the value of ultrasonography in the assessment of thyroid gland morphology and its role as a useful imaging tool in the prevention of potential mental retardation in CH patients by avoiding treatment initiation delay [15], which was also reported recently by Nasri et al. in Isfahan [16], the aim of this study was to determine the ultrasonographic findings of thyroid glands in CH patients in Isfahan.

Material and methods

In this cross-sectional study, newborns referred to Isfahan Endocrine and Metabolism Research Centre for treatment and follow-up with suspicion of CH on the basis of a screening program in Isfahan, from May 2002 to February 2009, were studied. From May 2002 to April 2005, serum T4 and TSH concentrations of all 3–7-day-old newborns, born in all 17 hospitals in the city of Isfahan, were measured by radioimmunoassay (RIA) and immunoradiometric assay (IRMA), respectively, using Kavoshyar (Iran-Tehran) kits. Thyroid function tests were performed by Berthold-LB2111 unit gamma counter equipment. Newborns with abnormal screening examination were re-examined, and those with abnormal T4 and TSH levels on their second measurement were diagnosed as CH patients, and received treatment and regular follow-up [10]. After implementation of a nationwide CH screening program in Iran from April 2005, screening was performed using filter paper, and neonates with TSH > 10 were recalled and those with abnormal T4 and TSH levels on their second measurement were diagnosed as CH patients, and received treatment and regular follow-up. Written consent was obtained from the parents of the CH patients.

Thyroid ultrasonography was performed in all CH patients during their follow-up. Ultrasonography was always performed by the same physician (H SM). Thyroid ultrasonography of the entire neck was performed prospectively with the patient in supine position, in the transverse and longitudinal planes, with the neck hyper-extended, using a Honda (Japan) ultrasonographic device, with an HLS — 475 M, 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 ectopy was defined as the presence of thyroid tissue of localization other than 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 [11].

The volume of the thyroid gland was assessed in all neonates. Transverse (X), sagittal (Y), and anteroposterior (Z) lengths of the right and left lobes were measured and volumes (V) calculated by three-dimensional ellipsoid formula ($V = 0.52 \times X \times Y \times Z$) and expressed in millilitres (17). The sum of the volumes of both lobes was taken as the total thyroid volume. The isthmus was not taken into account in thyroid volume calculations. The mean thyroid volume in CH patients with normal thyroid ultrasonography was compared with the mean thyroid volume in healthy newborns, evaluated by Adibi et al. [11] (unpublished data). According to their study, the median thyroid volume in

CH patients was 0.8 mL and mean thyroid volume in healthy control group was 1.2 ± 0.4 mL. A thyroid gland of volume exceeding mean + 2SD was considered goitrous.

Statistical analysis

The obtained data was analysed using SPSS v. 13. For variables without normal distribution, the median was presented. For all other variables with normal distribution, data were presented as mean ± SD. Log transformation was used in order to reduce skewness.

The mean values of the studied variables between the groups was compared using the ANOVA test. If it was statistically significant then the *post hoc* test was used to know which of the two groups were different. The median of the studied variables between the groups was compared using the Kruskal-Wallis Test. P-values < 0.05 were considered statistically significant.

Table I. *Baseline characteristics of congenitally hypothyroid neonates studied by ultrasonography*

Tabela I. *Wyjściowa charakterystyka grupy niemowląt z wrodzoną niedoczynnością tarczycy, u których wykonano badanie ultrasonograficzne*

Congenital hypothyroid neonates (n = 384)	Mean ± SD	Median
Age (months)	9.6 ± 9.7	
Female/Male	172/175	
*Screening TSH [mIU/L]	41.9 ± 52.0	23.5
*T4 [μg/dL]	8.2 ± 9.6	7.7
Total volume of thyroid gland [mL]	0.78 ± 0.44	
Right lobe [mL]	0.38 ± 0.22	
Left lobe [mL]	0.39 ± 0.23	
Rate of parental consanguinity (%)	36.4%	

*Variables without normal distribution were presented as medians and other variables with normal distribution as means ± SD

Results

In this study, 384 children aged 0-3 years old, with both transient and permanent CH were studied. Baseline characteristics of the studied population are presented in Table I.

The mean thyroid volume in boys and girls was 0.81 ± ± 0.4 mL and 0.73 ± 0.39 mL, respectively (p > 0.05).

There were 30 infants (aged below 30 days) among the studied children. The mean thyroid volume in infants was 0.71 ± 0.38 mL. According to ultrasonographic findings, 28 infants had normal thyroid and 2 had thyroid hemiagenesis. The mean thyroid volumes were 0.73 ± ± 0.38 mL and 0.41 ± 0.06 mL in the normal and hemiagenesis groups, respectively.

The ultrasonographic findings among the studied population were as follows: 80.1% (n = 278) normal thyroid , 12.7% (n = 44) thyroid agenesis,1.4% (n = 5) thyroid ectopy, and 5.8% (n = 20) thyroid gland hemiagenesis. Overall, 19.9% had thyroid dysgenesis (thyroid agenesis, ectopy, or hemiagenesis) and the reminder (80.1% had normal thyroid glands.

The characteristics of congenitally hypothyroid neonates with thyroid dysgenesis and normal thyroid glands are presented in Table II.

Thyroid dysgenesis was more prevalent in females and normal thyroid in males. The characteristics of congenitally hypothyroid neonates with thyroid dysgene-

Table II. *Characteristics of congenitally hypothyroid neonates with thyroid dysgenesis and normal thyroid gland regarding ultrasonographic findings*

Tabela II. *Charakterystyka niemowląt z wrodzoną niedoczynnością tarczycy z dysgenezją lub prawidłowym obrazem narządu w badaniu ultrasonograficznym*

	Normal thyroid gland (n = 287)	Thyroid dysgenesis (n = 69)	p value
Age (months)	9.6 ± 9.5	9.7 ± 10.5	NS
Female/Male	125/153	47/22	p < 0.05
*Screening TSH [mIU/L]	22.9	34	p = 0.07
*T4 [μg/dL]	7.9	6.5	NS
Total volume of thyroid gland [mL]	0.78 ± 0.44	0.62 ± 0.20	NS
Right lobe	0.38 ± 0.22	0.35 ± 0.19	NS
Left lobe	0.39 ± 0.33	0.33 ± 0.17	NS
Rate of parental consanguinity (%)	39%	27.9%	NS

*Variables without normal distribution were presented as medians and other variables with normal distribution as means ± SD

Table III. *Characteristics of congenitally hypothyroid neonates with thyroid dysgenesia (agenesis, ectopy, and hemiagenesis)*
Tabela III. *Charakterystyka niemowląt z wrodzoną niedoczynnością tarczycy, u których stwierdzono dysgenezję tego narządu (agenezja, ektopia, hemiagenezja) w badaniu ultrasonograficznym*

	Agenesis (n = 44)	Ectopy (n = 5)	Hemiagenesis (n = 20)	p value
Age (months)	8.7 ± 10.3	13.1 ± 10.6	10.2 ± 10.3	NS
Female/Male	29/15	3/2	15/5	$p < 0.05$
*Screening TSH [mIU/L]	47.5	100	23.2	$p<0.05$
*T4 [mg/dL]	6	7.6	10.8	NS
Total volume of thyroid gland [mL]	–	0.54	0.62	NS
Right lobe	–	0.24	0.18	NS
Left lobe	–	0.29	0.29	NS
Rate of parental consanguinity (%)	34.5%	0%	16.7%	NS

*Variables without normal distribution were presented as medians and other variables with normal distribution as means ± SD

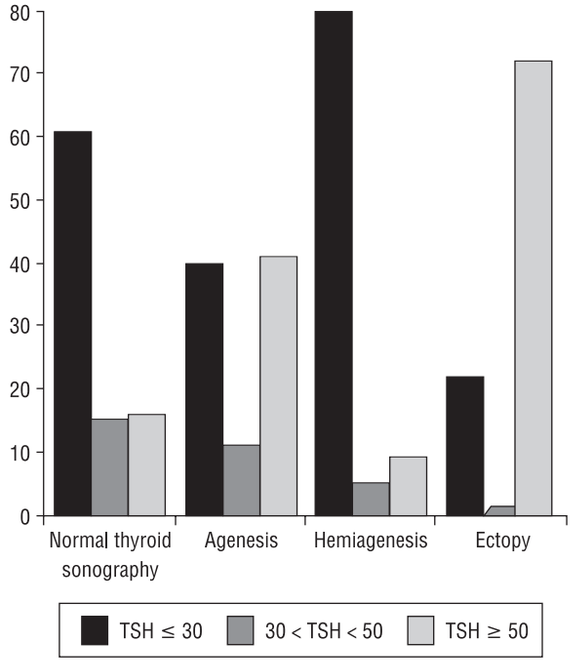

Figure 1. *Prevalence of different aetiologies of CH according to different screening TSH ($p < 0.05$)*

Rycina 1. *Występowanie CH o zróżnicowanej etiologii w zależności od stężenia TSH w badaniu przesiewowym ($p < 0,05$)*

sis regarding different aetiologies, i.e. agenesis, ectopy, and hemiagenesis, are presented in Table III.

The prevalence of different aetiologies of CH according to different screening TSH levels is presented in Figure 1. There was a significant correlation between thyroid volume and TSH and T4 ($p < 0.05$). There was a significant correlation between TSH and the aetiology of CH determined by ultrasonography ($p < 0.05$).

Discussion

Despite the fact that neonatal screening programs for CH are capable of early diagnosis of the disorder, the role of thyroid imaging in determining the aetiology of CH is extremely important [2]. Therefore, in this study we present the ultrasonographic findings of CH patients in Isfahan. The results of the current study indicate that the most common cause of CH is thyroid dyshormonogenesis, and thyroid dysgenesis is considered for only 19.9% of CH patients, which was not similar to previous reports in the field of CH aetiology in other countries.

The most common cause of CH worldwide is thyroid dysgenesis, which accounts for 85% of all cases of CH, and dyshormonogenesis accounts for the remaining 15% [18]. The results were in line with the reports of Hashemipour et al. [19] in Isfahan and Ordookhani et al. in Tehran [20].

The findings of the current study provide an important argument for the genetic background of thyroid dysgenesis and an important reason for the differences in CH incidence in comparison to other countries in Europe or the USA. The significant difference in aetiological factors of CH in the Iranian population should be underlined, when compared to previous studies, where 85% of CH is caused by thyroid developmental anomalies [18].

On the other hand, it is unwarranted to assume that all the patients with bilobed thyroid have dyshormonogenesis; however, some normal thyroid glands in sonography do not exhibit appropriate uptake in the scintiscan and may be interpreted as thyroid agenesis based on isotope examination [15]. To state this, genetic studies should be performed for confirmation.

It is also worth mentioning that in this study the rate of consanguinity did not differ significantly between patients with bilobed thyroid and those with thyroid dysgenesis. This might be due to the small sample size, but as previously mentioned, further genetic studies are recommended in this field.

Hashemipour et al. investigated permanent and transient CH in patients after 3 years of treatment and follow-up [19]. According to their results, 50.9% of permanently hypothyroid patients had dyshormonogenesis and 49.1% had dysgenesis, and in contrast to many studies (and likewise our study), agenesis was more prevalent than ectopy among patients with dysgenesis. In the current research, considering that the studied population included patients 0–3 years old, subjects with permanent and subjects with transient forms of CH were included. Thus, patients with bilobed thyroid comprise subjects with the transient form of CH as well as subjects with dyshormonogenesis.

Moreover, the high proportion of patients with thyroid hemiagenesis is striking as authors to date have reported a very low prevalence of patients with hemiagenesis (at the rate of 1%) among children with CH. This might be because in the study, children with transient and children with persistent CH were involved, while thyroid hemiagenesis causes the transient form of hypothyroidism. Ruchala et al. have reported that most adult patients with thyroid hemiagenesis maintain clinical euthyroidism [21].

The usefulness of ultrasonography in studies on the aetiology of CH has been proven, especially during the initial evaluation of CH patients. Many studies support the use of sonography instead of scintiscan in diagnosing children with CH because of its high cost, irradiation, lack of parental consent, and low sensitivity in distinguishing goitrous from non-goitrous hypothyroidism of thyroid scintiscan [15]. Ramos et al. reported that in studies employing thyroid scintiscan, ectopy is the most common cause because ultrasound examination does not reveal small foci of functioning thyroid ectopic tissue [22].

Recently Nasri et al. [16], in their study in Isfahan among CH patients, concluded that thyroid ultrasonography is a relatively appropriate imaging tool for diagnosing thyroid dysgenesis. It can be used as the first imaging tool for diagnosing CH, especially when the family prefers not to have the infant scanned. It is also considered as a non-invasive method for the anatomical evaluation of the thyroid gland and for determining its volume, especially in childhood epidemiological studies. Moreover, ultrasonography of the thyroid gland provides valuable information about the iodine status of the children [23–24].

It seems that the most important finding is that the aetiology of CH in our community with a high rate of CH is different than that found in other studies ,which emphasizes the necessity of more aetiological studies, although some previous studies in this region have indicated probable genetic and environmental factors [11]. The findings of this study regarding thyroid volume may give us more informative data relating to the iodine status of the studied population and its relation to CH aetiology. In spite of the fact that one of the limitations of our study was that urine iodine was not measured in the studied population, the low rate of goitrous thyroid gland in patients with normal thyroid glands (4.8%) indicated that iodine deficiency could not explain the high rate of CH in our community.

The results of our study were in accordance with the study of Kojima et al. in Japan [25]. They studied 97 newborns with positive screening results for CH and reported the ultrasonographic findings of the studied population. According to their report, 85% had normal thyroid gland and 7.2%, 5.2%, and 2.1% had thyroid dysgenesis, enlarged thyroid, and hemi-hypoplasia, respectively.

The findings of this study regarding thyroid volume in CH patients were reported for the first time during CH screening in Isfahan.

The mean thyroid volume in patients with normal thyroid was in the range reported by previous studies for this age group [26, 27]. In different studies, the thyroid volume in neonates ranged between 0.47 and 1.62 mL. Mean bilobed thyroid volumes for all male and female neonates were calculated as 0.82 ± 0.18 mL (range 0.51––2.04 mL) in a moderately iodine-deficient area in Turkey [24]. In another study in Colombia the mean estimated thyroid volume was 0.6 ± 0.2 mL for neonates and 1.1 ± 0.6 mL for milk-fed babies. The mean thyroid volume in infants and newborns in this study was similar to that found in the mentioned studies [28].

The mean thyroid volume of CH patients with normal thyroid was lower than the mean thyroid gland volume in healthy neonates in the study of Adibi et al. (unpublished data). It seems that it is due to the fact that ultrasonography has limited value for the evaluation of thyroid gland function, so it may identify an anatomically normal but non-functional thyroid gland which is probably smaller than a normal functioning gland [29]. However, more studies with larger sample sizes, especially for healthy neonates, are needed to determine the mean thyroid volume, as well as for CH patients with normal sonographic results, especially with combined sonographic assessment [30].

Thyroid ultrasonographic findings such as thyroid volume and different aetiologies of CH were associat-

ed with screening TSH in the studied CH patients in the current study. Kojima et al. reported similar results in their study and they concluded that ultrasonography should be considered a valuable imaging tool in CH screening programs. On the other hand, Koksal et al. in Turkey reported that there were no statistically significant differences in thyroid volumes regarding to TSH values of neonates [27].

In conclusion, in spite of the limitations of ultrasonography in the field of determining the aetiology of CH, it is an appropriate imaging tool for determining the volume of thyroid glands in children and for initial evaluation of newly diagnosed patients with CH, because of its association with thyroid function tests, especially TSH. On the other hand, considering that the rate of goitrous gland was low, it seems that iodine deficiency could not be responsible for the high rate of CH in this region [31].

However, more studies with larger sample sizes of CH patients with permanent CH, and in accordance with iodine and other trace element measurements, are needed for conclusions that are more accurate in this field. In addition, thyroid volume should be assessed in healthy neonates in a large sample size in order to determine local reference values.

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