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Original Article

Etiological Evaluation of Congenital Hypothyroidism in Cases Referred from the National Screening Program

Deniz Tanyeri[1], Ayşe Anık[2], Arzu Cengiz[3], Yasemin Durum Polat[4], Tolga Ünüvar[5], Ahmet Anık[5]

[1]Aydın Adnan Menderes University Faculty of Medicine, Department of Pediatrics, Aydın, Turkey
[2]Aydın Adnan Menderes University Faculty of Medicine, Department of Neonatology, Aydın, Turkey
[3]Aydın Adnan Menderes University Faculty of Medicine, Department of Nuclear Medicine, Aydın, Turkey
[4]Aydın Adnan Menderes University Faculty of Medicine, Department of Radiology, Aydın, Turkey
[5]Aydın Adnan Menderes University Faculty of Medicine, Department of Pediatric Endocrinology, Aydın, Turkey

ABSTRACT

Aim: To evaluate cases referred from the congenital hypothyroidism (CH) new-born screening program.

Materials and Methods: One hundred and thirty-five cases which were referred between January 2017 and July 2019 were included in the study.

Results: Fourty eight of 135 cases (35.6%) were diagnosed as CH. The mean onset of treatment was 17.31±9.92 days. Clinical findings suggesting hypothyroidism were detected in 27 patients (56.2%) and goiter was detected in 2 patients (4.1%). According to imaging findings, 16 (35.5%) patients were diagnosed as dysgenesis, [1 (2.2%) as agenesia, 3 (6.7%) as ectopia, and 12 (26.6%) as hypoplasia], 11 were diagnosed as dyshormonogenesis (24.5%), and 18 were diagnosed as eutopic thyroid (40%). The mean levothyroxine dose was 12.7±2.5 mcg/kg/day and the mean onset of treatment in 30.4% of diagnosed patients was within the first 14 days and 93.3% were within the first 30 days.

Conclusion: Dysgenesis and dyshormonogenesis are the most common detectable causes of CH. The normal localization of the thyroid gland in about half of the patients suggests that transient causes of CH may be more common than expected. Considering that only 1/3 of the patients were treated in the first 2 weeks, it was thought that the referral of patients is still an important problem and it should be done more promptly.

Keywords: Congenital hypothyroidism, neonatal screening program, etiology

Introduction

Congenital hypothyroidism (CH) is defined as the deficiency of thyroid hormones in newborn babies, with an incidence of 1 in 1,400 to 2,800 (1,2). Due to the essential role of thyroid hormones in brain development, its deficiency can have devastating effects on neurocognitive development if not detected and treated early and effectively (1). The lack of obvious clinical manifestations of hypothyroidism in newborns, reinforces the pivotal role of newborn screening in facilitating prompt diagnosis and treatment.

The most frequent method used for screening for CH in the world, as well as in our country, is the measurement

Address for Correspondence
Ahmet Anık MD, Aydın Adnan Menderes University Faculty of Medicine, Department of Pediatric Endocrinology, Aydın, Turkey
Phone: +90 256 214 54 00 E-mail: ahmet.anik@yahoo.com ORCID: orcid.org/0000-0002-7729-7872
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of thyroid stimulating hormone (TSH) from the heel-stick blood sample between the 2nd and 5th days of life (3). Screening for CH in Turkey was started in 2006 and the incidence of CH in Turkey was reported as 1 in 888 in 2008, 1 in 592 in 2009 and 1 in 469 in 2010 (4). Though the prevalence of CH in our country is not exactly known, various studies reported that transient CH varies between 25 and 65% (5-9). Considering the increasing frequency in recent years, it is becoming more important to determine the etiological factors of CH.

The aim of this study was to evaluate the rate of diagnosis of CH in referred patients from the national screening program; as well as the clinical and laboratory features and etiological distributions of the patients.

Materials and Methods

In this study, cases with high capillary TSH who were referred from the national screening program to our hospital were retrospectively evaluated. This study was carried out in Aydın province located in the Aegean region. The study was approved by the Aydın Adnan Menderes University Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee (date: 22.08.2019, approval number: 2019/125).

CH was diagnosed according to ESPE guidelines (10):

- Venous TSH level >20 mIU/L and fT4 level normal or low (<0.7 ng/dL)

- Patients whose venous fT4 level is within normal limits (0.7-1.48 ng/dL) and TSH level is between 6-20 mIU/L and those with normal fT4 levels and increased TSH levels underwent repeated weekly measurements until postnatal 21st day of life.

The demographic information of the patients, postnatal age, birth week, birth weight, family history of thyroid disease, consanguinity, physical examination and perinatal event details including complaint, anthropometric data, heel-stick blood sample time and results, and laboratory and imaging results were obtained from the hospital recording system. In addition, serum fT4, TSH, thyroglobulin (TG), ultrasonographic features (localization, volume, parenchymal echogenicity of the thyroid gland), and thyroid scintigraphy (localization and activity of the thyroid gland) and serum thyrotropin receptor antibodies (TRB-Ab) level in those patients with maternal thyroid disease were also recorded from the same data.

Laboratory and imaging tests of all patients were performed on the same day. TSH and fT4 were measured by chemiluminometric assay with Abbott Architect i2000. TG levels were measured by two different immunoassay methods (ROCHE cobas 601 and ROCHE cobas E411). The TRB-Ab level was measured by the radioimmunoassay method (STRATEC-GAMA READER and TRAC ETIMAX).

Thyroid ultrasonography was performed by the same pediatric radiologist using the L3-12A broadband high-resolution linear probe with a frequency range of 3-12 MHz with the Samsung Medison RS80A Prestige (Samsung Medison Co. Ltd., Seoul, Korea). The longest longitudinal (D1), anterior-posterior (D2), transverse (D3) diameter and isthmus thickness were recorded separately for both lobes of the thyroid gland. The volume for each lobe and the entire gland in millilitres was automatically calculated according to the formula [width x length x depth x $\pi/6$ (0.523)] in the Child Metrics program (11). Those volumes of thyroid gland between 0.526-1.849 mL for the entire gland, 0.228-0.931 mL for the right lobe, and 0.294-0.959 mL for the left lobe were considered as normal (12). Results below these values were considered as hypoplasia and above as hyperplasia.

Twenty minutes after 500-750 µCi Technetium-99m pertechnetate intravenous injection, thyroid scintigraphy was performed via a Siemens syngo via device and gamma camera and images were recorded for a total of 5 minutes. Anatomical localization of the gland and activity (decreased, increased, or normal) of these images were evaluated by the same nuclear medicine specialist.

Patients with agenesis, ectopia or hypoplasia according to imaging results were classified as dysgenesis; while patients with a history of consanguinity and increased activity in the thyroid gland, or with increased activity and hyperplasia were classified as dyshormonogenesis. The remaining patients were classified as eutopic thyroid, which could be transient CH. The given starting LT4 dose was recorded in mcg/kg/day.

Statistical Analysis

Kolmogorov-Smirnov test was used to test whether the quantitative variables are suitable for normal distribution. The groups were compared with two independent samples t-test for normally distributed variables and Mann-Whitney U test for abnormally distributed variables. Chi-square analysis was used to test whether there is independence between qualitative variables. Descriptive statistics of variables with normal distribution were expressed as "mean ± standard deviation" and descriptive statistics of abnormally distributed quantitative variables as "median (25th-75th percentile)". Descriptive statistics of qualitative variables were expressed in frequency (%). $P<0.05$ values were considered statistically significant.

Results

Of the 135 cases included in the study, 48 (35.6%) were diagnosed with CH, and 87 (64.4%) cases were healthy. The average age at admission was 19.05±9.87 days for the whole study population, and it was 17.3±9.9 days in those babies with CH. The average gestational week of the 48 patients with CH [19 (39.6%) female, 29 (60.4%) male] was 38.7±1.7 weeks, among which, 40 of the cases were term (83.3%) and 8 were preterm babies (16.7%). The mean birth weight was 3,130.1±455.3 g. There was no significant difference between the group diagnosed with CH and the healthy group in terms of age of presentation, birth week, birth weight, term/preterm rate, and gender distribution (p>0.05) (Table I). Body weight, height and head circumference at the time of presentation were similar in both groups.

The average first and second screening times of those patients diagnosed with CH was 6 (4-8) and 10 days (8-14), respectively. The average first screening of TSH level was 10.22 µIU/mL (6.47-17.69) and the second was 20.06 µIU/mL (9.5-25.63) (Figure 1). The average time to start treatment was 17±9 days in those patients with CH.

There was a family history of thyroid disease in 17 (34.4%) of those patients with CH, and history of consanguinity between parents in 11 (22.9%) cases. There were 4 patients with CH whose mother had hypothyroidism and TRB-Ab was negative in all of these babies. No significant difference was found between the group with CH and the healthy group in terms of family history of thyroid disease and consanguinity. Iodine exposure was present in 16 (11.9%) cases in the whole group and in 5 (10.4%) of those patients with CH. This exposure was due to iodine-containing antiseptics that were used for umbilical care in all cases.

The average TSH level at the time of diagnosis was 62.94±49.33 µIU/mL in the CH group, and 3.1 µIU/mL (0.77-4.81) in the control group. The average fT4 level was 0.63 ng/dL (0.22-1.22) in the CH group; and 1.09±0.14 ng/dL in the control group. Thirty patients (62.5%) with CH had low fT4 levels (<0.7 ng/dL) at the time of diagnosis. Serum TSH and fT4 levels at the time of admission were statistically significant between the two groups (p<0.001) (Table II).

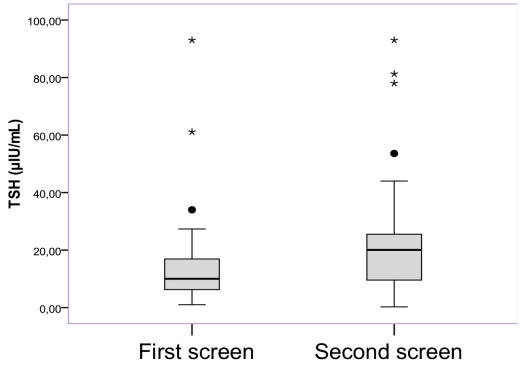

Figure 1. The first and second heel-stick TSH levels in patients with congenital hypothyroidism

TSH: Thyroid stimulating hormone

Table I. Anthropometric, demographic and clinical features of the subjects

		All group n=135 (%)	Congenital hypothyroidism n=48 (%)	Healthy group n=87 (%)	p
Gender	Male	80 (59.3)	29 (60.4)	51 (58.6)	0.984
	Female	55 (40.7)	19 (39.6)	36 (41.4)	
Gestational week	Preterm	30 (22.2)	8 (16.7)	22 (25.3)	0.349
	Term	105 (77.8)	40 (83.3)	65 (74.7)	
Birth week (week)		38.4±1.7	38.7±1.7	38.3±1.7	0.138
Birth weight (gram)		3163.6±474	3130.1±455.3	3182.1±485.6	0.544

Table II. fT4 and TSH levels at admission

	All group n=135	Congenital hypothyroidism n=48	Healthy group n=87	p
TSH (µIU/mL)	24.33±41	62.94±49.33	3.1 (0.77-4.81)	<0.001
sT4 (ng/dL) Low (<0.7 ng/dL) Normal (>0.7 ng/dL)	0.93±0.27 30 (22.2%) 105 (77.8%)	0.63 (0.22-1.22) 30 (62.5%) 18 (37.5%)	1.09±0.14 0 (0%) 87 (100%)	<0.001

TSH: Thyroid stimulating hormone

Thirty three out of 48 patients (68.8%) had symptoms suggesting CH; jaundice in 18 (37.5%), poor sucking in 9 (18.8%), and constipation in 6 cases (12.5%). On physical examination, coarse face was detected in 3 (6.3%), umbilical hernia in 2 (4.2%), jaundice in 18 (60%), and goiter in 2 (4.1%) cases.

Thyroid USG was performed in 44 (91.7%) out of 48 cases, and thyroid scintigraphy in 45 (93.8%) cases. In 4 (9%) cases, the thyroid gland in USG could not be visualized at normal localization. One of them was diagnosed with agenesis; and the other 3 patients were diagnosed as sublingual ectopic thyroid gland according to thyroid scintigraphy. The total volume of the thyroid gland in the other cases was calculated as 1.93±3.7 mL, right lobe 1±1.2 mL, left lobe 1±1.9 mL. Hypoplasia was detected in 11 cases (25%), normal thyroid gland in 20 cases (45.5%), and hyperplasia in 9 cases (20.5%) according to USG. Thyroid scintigraphy showed normal activity in 11 (8.1%), increased activity in 23 (17%), decreased activity in 4 (3%) cases, and 4 (2.9%) cases without gland involvement.

According to etiological classification, 16 patients (35.5%) were classified as dysgenesis [1 agenesis (2.2%), 3 ectopia (6.7%), 12 hypoplasia (26.6%)]; and 11 cases (24.5%) as dyshormonogenesis. The remaining 18 (40%) cases were classified as eutopic thyroid gland (Table III).

The average age at the beginning of the treatment was 17.3±9.9 days and the dose of LT4 was 12.7±2.5 mcg/kg/day.

Discussion

In this study, babies who were referred from the national screening program during a 2-year-period were retrospectively analysed, and CH was diagnosed in 48 (35.6%) out of 135 cases. This rate was reported as 44% in another study conducted in our country, which is compatible with our study (5). In this study, approximately 2/3 of those cases diagnosed with CH were male. In many studies, it has been reported that CH is more common in girls (13,14). However, in recent studies, male dominance has been reported, similar to our study (15-17). Since dysgenesis is known to be more frequent in girls and the rate of dysgenesis is relatively low in our study, it was thought that the higher frequency of males could be related to reasons other than dysgenesis.

Bongers-Schokking et al. (18), reported that neurodevelopmental outcomes of babies with CH that were treated in the first two weeks were similar to a healthy group. In our study, approximately one third of the cases were admitted within the first 14 days of life and the average age of diagnosis was 17 days. In the study of Kor and Kor (15), the average age of admission was found to be 19.87±7.63 (4-51) days and the rate of diagnosis in the first month was 88.4%. Peltek Kendirci et al. (5) reported that the average age of diagnosis was 19.7±8.30 (5-60) days and this is similar to our study. Eren et al. (19) reported the average age of diagnosis before and after the screening program to be 292 and 35 days, respectively. Although the time of diagnosis

Table III. Etiological distribution of patients with congenital hypothyroidism (n=45)

Etiology		Ultrasonography	Scintigraphy
1. Dysgenesis: n=16 (35.5%)			
Agenesis: n=1 (2.2%)		No thyroid gland	No uptake
Ectopia: n=3 (6.7%)		No thyroid gland	Sublingual thyroid gland
Hypoplasia: n=12 (26.6%) Normal: 1		Hypoplasia: 11	Decreased activity: 3 Normal activity: 1 Normal activity: 4 No uptake: 3
		Decreased activity: 1	
2. Dyshormonogenesis: n=11 (24.5%)			
Consanguinity	Yes: 7	Increased activity: 7	
	No: 4	Hyperplasia: 4	Increased activity: 4
3. Eutopic thyroid: 18 (40%)			
n=18 Hyperplasia: 2 Normal: 5		Normal: 10*	Increased activity: 11
		Normal activity: 7	

*One patient with increased activity in scintigraphy had no USG images
USG: Ultrasonography

after the screening program shifts significantly to earlier, according to many studies, the diagnosis rate is still very low in the first two weeks of life.

In this study, the venous TSH value was significantly higher in CH patients compared to the healthy group. In a study by Peltek Kendirci et al. (5), the mean venous TSH level was 55.2±33.5 µIU/mL (0.77-4.81) in patients with CH. Similarly, in a study conducted in 223 patients with CH, it was reported that the mean venous TSH level was 67.26 µIU/mL (15). In our study, venous TSH and fT4 levels at the time of diagnosis were similar to many studies in the literature.

The most common symptom in our patients with CH was jaundice. Similar to our study, Özgelen et al. (20) reported that prolonged jaundice was the most common symptom in patients with CH.

In our study, the most common cause of CH was eutopic thyroid gland (40%), followed by thyroid dysgenesis (35.5%) and dyshormonogenesis (24.5%). In one recent study, the etiological distribution of CH was reported as 33.3% dysgenesis (commonly hypoplasia), 33.3% dyshormonogenesis and 16 (33.3%) as "possible dyshormonogenesis and transient hypothyroidism" (21). In a study conducted in Egypt with 248 patients, 161 (65%) of the cases were diagnosed with dysgenesis (107 ectopic, 28 agenesis, 26 hypoplasia), and 87 (35%) of them with dyshormonogenesis (22). Since the etiological distribution is multifactorial; dysgenesis, dyshormonogenesis and eutopic thyroid rates differs among studies. Methodological differences are thought to be the most important reason for the etiological differences among these studies: (i) some studies used thyroid ultrasonography while others used thyroid scintigraphy for the definition of dysgenesis, and (ii) the diagnosis of dyshormonogenesis was not molecularly confirmed in most studies, hence, these factors significantly affect the etiological distribution. In addition, the frequency of transient hypothyroidism is increasing gradually. In studies published in our country, the frequency of transient hypothyroidism has been reported to be between 25-65% (23). Although the frequency of transient hypothyroidism was not defined in our study, it can be predicted that many cases with eutopic thyroid gland will be transient (24). One of the most important reasons for the increased frequency of transient hypothyroidism in recent years is the lowering of the screening TSH cut-offs. The lowering of the screening TSH cut-offs in these programs has been associated with the doubling of CH incidence, primarily explained by the detection of milder cases. While the whole blood TSH cut-off value in Turkey was 20 µIU/mL in the past, it was determined to be 10 µIU/mL at the start of the screening program, and was lowered to 7.5 µIU/mL in 2009 (4,6,24-26). Accordingly, the frequency of transient CH increased from 27% to 56% in a period of ten years in our country (23).

Study Limitations

There are some limitations in our study: (i) the etiological distribution of CH was made according to the imaging findings, and molecular confirmation tests required for the definitive diagnosis of dyshormonegenesis could not be performed and (ii) Urinary iodine excretion could not be performed, so iodine excess or iodine deficiency could not be documented. The strengths of the article are; (i) it is single centre trial, (ii) the data are complete, (iii) and the imaging methods are standard and were assessed by the same physician.

Conclusion

The most common detectable causes of CH were shown to be dysgenesis and dyshormonogenesis. Considering that the thyroid gland is eutopic in approximately half of the cases, transient causes of CH might be higher than expected. Although the duration until diagnosis and initiation of treatment of CH were markedly reduced with the implementation of the screening program in Turkey compared to before the implementation of the screening program, the targeted and ideal time has not yet been reached for final diagnosis and the initiation of treatment (≤2 weeks).

Ethics

Ethics Committee Approval: The study was approved by the Aydın Adnan Menderes University Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee (date: 22.08.2019, approval number: 2019/125).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Design: T.Ü., A.A., Data Collection or Processing: D.T., A.C., Y.D.P., Analysis or Interpretation: D.T., A.A., A.C., Literature Search: Ay.A., Writing: T.Ü.

Conflict of Interest: No conflict of interest was declared by the authors.

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