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Original article

The Evaluation of Etiological Distribution and the Rate of Congenital Hypothyroidism among the Cases Referred from National Screening Program

Short Title: Screening for congenital hypothyroidism

Zeynep Donbaloglu[1], Şenay Savaş-Erdeve[2], Semra Çetinkaya[2], Zehra Aycan[2]
[1]Dr. Sami Ulus Obtetrics and Gynecology, Children's Health and Disease Training and Research Hospital, Pediatrics, Ankara, Turkey
[2]Dr. Sami Ulus Obtetrics and Gynecology, Children's Health and Disease Training and Research Hospital, Pediatric Endocrinology, Ankara, Turkey

ABSTRACT

Objective: The aim of this study was to evaluate cases referred from congenital hypothyroidism screening program.
Methods: Infants referred to Pediatric Endocrinology Polyclinic between 30.09.2015 - 01.04.2018 dates, because of suspected congenital hypothyroidism within the scope of Ministry of Health National Neonatal Screening Program were prospectively evaluated.
Results: Of the 109 newborns referred to our clinic, 60 (55%) were diagnosed with CH. The diagnosis of CH were both done in 52 (47.7 %) and 8 (7.3 %) infants as a result of the initial evaluation and follow up. The mean first and second heel prick times were 1.8 (0 - 7) and 8.72 (4 - 30) days. The mean age of the 52 infants whose treatment was initiated as a result of initial evaluation was 22.13 (7 - 53) days. There were clinical findings can be releated to hypothyroidism in 19 (%36) patients. There was agenesis in 1 (2.08%) patient, ectopia in 1 (2.08%) patients, hypoplasia in 14 (29.16%) patients, normal gland in 16 (33.3%) patients and hyperplasia in 16 (33.3%) patients diagnosed with CH on admission. TSH and fT_4 level normalization time after the treatment was 11.02(4 - 30) days and 9.03(3 - 30) days, respectively.
Conclusion: The rate of diagnosis in the first month was found to be 87%. The mean time of initiation of treatment was 22(7-53) days. Dysgenesis rate was 33.3% and dyshormonogenesis rate was 33.3%. The majority of cases with normal thyroid gland will be diagnosed with transient hypothyroidism but some of them may be diagnosed with thyroid dyshormonogenesis.
Keywords: Congenital Hypothyroidism; Neonatal Screening Program; Newborn; Thyroid Hormones

Corresponding author: Şenay Savaş-Erdeve, MD.
Associate Professor, Dr. Sami Ulus Obstetrics and Gynecology, Children's Health and Disease Training and Research Hospital
Plevne Mahallesi, Babür Caddesi, No:36-38 (06080) Altındağ ANKARA
Phone: +90 (312) 305 65 39 Fax: +90 (312) 317 03 53
e-mail: senaysavas@yahoo.com

What is already on this topic?
Congenital hypothyroidism is the most commonly seen endocrinological disorder of childhood period in the world.
The increase in the prevalence of CH has been reported worldwide in the last 20 years.

What this study adds?
The rate of CH was found to be 55% and it is seen that approximately one of every 2 cases who were referred from national screening program was diagnosed with CH.
The rate of diagnosis in the first month was found to be 87%. Dysgenesis rate was 33.3%.

INTRODUCTION

Congenital hypothyroidism is the most commonly seen endocrinological disorder of childhood period in the world. The incidence of CH was found to be 1/4000 in the 1970s when the screening program was firstly used. In the last 20 years, increase in the prevalence of CH has been reported worldwide (1).
In a study conducted by Hacettepe University Ihsan Dogramacı Children's Hospital Pediatric Endocrinology Unit in 2003, the incidence of permanent CH was found to be 1/2512 (2). In an evaluation between the years 2008 and 2010 reported that, the incidence of CH was found to be 1/888 in 2008, 1/592 in 2009, and 1/650 in 2010 (3).

The absence of the disease-specific clinical manifestation in CH at the birth and prevention of complications with the early initiation of treatment when the diagnosis was made within the first few weeks after the delivery, effectiveness and inexpensiveness of treatment, made the necessity of screening program a current issue. CH screening program was first implemented in 1974 in Quebec, Canada, Pittsburgh and Pennsylvania (4,5). In our country, although local scans have been made before; CH screening conjunction with phenylketonuria screening has been implemented for the first time on 25 December 2006 in general of Turkey (6,7).
In our country, TSH threshold value was determined as 20 mIU/L in the first years of screening and it was decreased to 15 mIU/L in January 2009 upon detection of cases without diagnosis. **In 2016, TSH threshold value was updated to 20 mIU/L (3,8).**
In this study, we aimed to detect the rate of diagnosis with CH and the time of diagnosis in cases referred from screening program; evaluate the clinical and laboratory findings and determine the etiological distribution among the patients diagnosed with CH.

SUBJECTS AND METHODS

Analysis results of infants referred to Health Sciences University Ankara Dr. Sami Ulus Maternity, Children Health and Disease, Health Application and Research Center, Pediatric Endocrinology Polyclinic between 30.09.2015 - 01.04.2018 dates, because of suspected congenital hypothyroidism within the scope of Ministry of Health National Neonatal Screening Program were prospectively evaluated. The ethics committee approval of study was received on 29.09.2015 from Zekai Tahir Burak Women's Health, Education and Research Hospital Clinical Research Ethics Committee. Before the study, all patients were informed with an informed consent form and taken sign for voluntary participation.
In our country with the scope of CH national screening program; infant is considered to have passed the screening test when the TSH level of less than 5.5 mIU/L in the blood sample taken to the filter paper. In the values between 5.5 mU/L and 20 mIU/L, the blood sample is taken to the filter paper again. All cases with a TSH level above 5.5 mIU/L in repeated blood sample or above 20 mIU/L in the first blood sample; are directed to the appropriate centers for examination of serum T_4 and TSH levels, by using family contact informations in the registration form filled in when heel prick blood sample was taken. In our study, serum T_4 and TSH levels were measured on the same day. Diagnosis and treatment plan was based on European Society for Pediatric Endocrinology Guideliness of Congenital Hypothyroidism (9).
The date of birth, date of admission, postnatal age, gender, birth week, type of delivery, birth weight were learned in all cases who were included in the study. Numbers, times and results of heel prick tests were recorded. All cases were investigated about family and maternal history of thyroid disease and moreover family history of CH. Consanguinity between parents was questioned. The presence of iodine exposure in the mother and the baby and the iodine status of the salt used during pregnancy were learned.
Body weight, height and head circumference were measured on admission. All patients were examined for clinical findings releated to CH. Letargy, inactivity, hypotonia, difficulty in feeding, falling asleep, constipation, abdominal distention, umbilical hernia, prolonged jaundice, galactorrhea, weak voice crying, hypothermia, cutis marmoratus, nasal congestion, whether dry and coarse skin structure were questioned. Physical examination was made for both additional congenital abnormalities and goiter. Serum thyroglobulin, TRB-Ab and spot urinary iodine levels were measured in patients diagnosed with CH. The thyroid gland localization, volume and parenchymal echogenicity were evaluated by thyroid ultrasonography. The thyroid gland localization and activity were evaluated by thyroid scintigraphy.
Serum TSH, **fT_4**, and **fT_3** levels were measured by chemiluminometric method on AdviaCentaur XP device. The thyroglobulin level was measured by immunoassay method on the Siemens Immulite 2000 analyzer device with the immulite 2000-thyroglobulin kit. TRB-Ab level was measured on the Bertholol 1B2111 device by radioimmunassay method with Beckmann Coulter RRA Anti-R TSH kit and spot urinary iodine level was measured on Agilent 7500 ICP-MS device by using ICP-MS analysis technique.
Thyroid USG was performed by specialist radyologist by using 7.5-MHz linear probe with Toshiba Alpro 500 device at the radiology department of our hospital. The thyroid volume was calculated for each lobe using the following formula: (D1xD2xD3/1000)x0.523 (D1:longest longitudinal, D2:anteroposterior and D3:largest transverse diameters in cm for each lobe) and the total volume was determined with sum of two lobes in ml. Thyroid volumes for the neonatal period with a 10th percentile value of less than 0.64 ml in patients were considered with hypoplasia, the 97th percentile value of 1.15 ml above the patients with hyperplasia and between 0.64 ml and 1.15 ml in patients with normal thyroid gland (10). Thyroid scintigraphy was performed in the Nuclear Medicine Department of our hospital using General Electric Millenium device and gamma camera with technetium 99 pertechnetate (Tc99).

Statistical analysis

In the presentation of descriptive statistics; the data obtained by measurement were expressed as mean±standard deviation and (minimum - maximum) and categorical data as number (percentage). Cross-table analyzes, Pearson and Fisher's exact Chi-square tests were used to compare the qualitative characteristics of the groups. Compatibility to normal distribution of the numerical measurements in the groups was examined by Shapiro

Wilks test. Comparision of two groups was made with t-test in independent groups for those with normal distribution in numerical measurements, and with Mann-Whitney U test for those without normal distribution. IBM SPSS (IBM Statistical Package for the Social Sience) 22 program was used for all statistical analyzes. P value of <0.05 was considered statistically significant.

RESULTS

Of the 109 newborns referred from the neonatal screening program; 52 (47.7%) at initial evaluation and 8 (7.3%) at follow up, a total of 60 (55%) infants were diagnosed with CH. Twenty nine (48.3%) of patients with CH were female, 31 (51.7%) were male and female to male ratio was 1:1.07. Gender, birth week, term/preterm rate, type of delivery, birth weight were similar in patients with CH compared to healty group (Table 1). Parental consanguinity rate was found to be 31.7% (19/52) in patients with CH and 8.16% (4/49) in healthy group. Parenteral consanguinity rate was significantly higher CH cases (p=0,004). The family history of thyroid disease, family history of CH, the rate of iodized salt consumption and iodine exposure were similar in patients with CH compared to healty group (Table 2).

Of the 100 patients (91.74%) in whole group, the heel prick test was performed twice. The mean number of heel prick test was similar in patients with CH and healthy group. The first heel prick time was 1.97±1.58 days, the second heel prick time was 8.5±4.62 days, and the third heel prick time was 15.9±5.43 days in whole group. The mean age at diagnosis was 30.2±24.8 days in all CH patients; 22.13±10.35 days in 52 (86.7%) patients diagnosed as a result of initial evaluation and 82.62±28.53 days in 8 (13.3%) patients diagnosed at follow up. According to results of patients diagnosed at initial evaluation, it was seen that 2 (4%) patients were diagnosed within the first 7 days, 3 (6%) patients between 8 and 14 days, 40 (76%) patients between 15 and 28 days and 7 (13%) patients later than 28 days. The rate of diagnosis and initiation of treatment in the first month was found to be 87%. Duration between the second heel prick time and the diagnosis was 13.98 ± 9.97 days.

There were clinical findings can be releated to hypothyroidism in 19 (36%) of 52 infants diagnosed as a result of initial evaluation. There were lethargy in 2 (10.5%) patients, feeding difficulty in 3 (16.78%) patients, constipation in 6 (31.5%) patients, constipation and umblical hernia in 1 (5.26% patient, prolonged jaundice in 6 patient (31.5%) and weak voice crying in 1 (5.26%) patient. There were no clinical findings in patients diagnosed at follow up. Goiter was detected on physical examination in 2 patients diagnosed as a result of initial evaluation. There were concomitant abnormalities in 11 patients (18.2%) of all CH cases (4 ASD, 1 PS, 1 hydrocephaly and meningomyelocele, 2 developmental dysplasia of hip, 3 Down syndrome). Patients with Down syndrome were accompanied by diagnosis of ASD, PDA and VSD.

Body weight, height and head circumference were similar on admission in patient diagnosed with CH and healthy cases. The mean TSH level was 71.05±59.2 µIU/mL, mean **fT_4** level was 0.83±0.35 ng/dL and mean **fT_3** level was 3.44±1.03 pg/mL in patients diagnosed with CH. The **fT_4** level was low in 33 (55%) patients (<0.9 ng/dL) and normal in 27 (45%) patients (>0.9 ng/dL) on admission (Table 3).

Urinary iodine levels could be measured in 29 patients and thyroglobulin levels in 35 patients diagnosed as a result of initial evaluation. Urinary iodine level was normal in 9 (31%) patients and high in 20 (69%) patient; thyroglobulin level was normal in 5 (14.3%) patients and high in 30 (85.7%) patients. TRB-ab level could be measured in 36 patients and it was negatif in 32 (88.8%) patients, borderline positive in 2 (5.6%) patients and positive in 2 (5.6%) patients.

Thyroid USG was performed for 49 infants diagnosed with CH. The mean thyroid gland volume was 1.06±0.95 (0 - 3.74) ml. In 3 (6.12%) cases, the thyroid gland was not visualized in normal location. One of these patients found to have sublingual ectopic thyroid gland and one of these patiens found to have agenesis on thyroid scintigraphy. Thyroid scintigraphy couldn't performed for one these patients and the thyroglobulin value was normal (16 ng/mL) in this case, so it was thought that there might be an ectopic thyroid gland or inactivating mutation at TSH receptor. There was hypoplasia in 14 (29.16%) patients, normal gland in 16 (33.3%) patients and hyperplasia in 16 (33.3%) patients. Ectopic thyroid gland rate was found to be 2.08% (1/48), agenesis rate was 2.08% (1/48), hypoplasia rate was 29.1% (14/48) and total of thyroid dysgenesis rate was found to be 33.3% (16/48). Sixteen patients (33.3%) with hyperplastic thyroid gland were diagnosed as dyshormonogenesis, 16 patients (33.3%) with normal thyroid gland were diagnosed as transient hypothyroidism and possible **dyshormonogenesis.** The time of diagnosis, consanguinity rate, TSH, **fT_4**, thyroglobulin and spot urinary iodine levels were similar in these three groups.

Levothroxine was started with the dose of 9.34 (2.10 – 15.0) µg/kg/d to patients diagnosed with CH as a result of initial evaluation. TSH level normalization time after the treatment was 11.02 (4 - 30) days by the age of postnatal 33.83 (13 - 70) days. **fT_4** level normalization time after the treatment in patients whose **fT_4** levels were low at diagnosis was 9.03 (3 - 30) days by the age of postnatal 31.4 (19 - 56) days.

DISCUSSION

In our study, 60 (55%) of 109 cases referred from the national screening program were diagnosed with CH. In a study conducted in our country, it was reported that 114 (44.5%) of 256 cases referred from national screening program were diagnosed with CH (11). In our study, female to male ratio was calculated as 1/1.07 in patients with CH. While previous studies have shown that female preponderance in female to male ratio in patiens with

CH as 1.8/1, 1.4/1 (12), it has been pointed out that the dominance of gender in recent years has shifted to male direction as 1:1.14, 1/1.16 (8,13).

In our study, the mean number of heel prick blood sample taken in the whole group within the scope of the Ministry of Health National Screening Program was 2.06. The first and second screening times were 1.97±1.58 (0 - 7) days and 8.5±4.62 (4 - 30) days. On admission to hospital, the mean age of the cases was found 27.47±14.2 (7 - 70) days in our study and 24.54±13.46 (4 - 168) days in the study of Kor et al (8). The mean age at diagnosis was 30.2 ± 24.8 days in all CH cases; 22.13±10.35 in patients diagnosed as a result of initial evaluation and 82.62±28.53 days in patients diagnosed at follow up in our study. Kor et al. reported in their study that 223 (96%) of all 233 patients were diagnosed as a result of initial evaluation and the mean age of diagnosis was 19.87±7.63 (4 - 51); 10 (4%) of patients were diagnosed at follow up and the mean age of diagnosis was 43.71±14.02 (29 - 65) days (8). The mean age of diagnosis was found as 19.7±8.30 (5 - 60) days in the study of Peltek Kendirci et al., 38.1±58 (4 - 342) days in the study of Kusdal et al. and 23±14 days in the study of Simsek et al. (11,14,15). Early diagnosis is the most important aim of the screening program. In our country, in a study comparing the pre-screenig and post-screening diagnosis time, it was mentioned that the time of diagnosis was 292 days before screening and it decreased to 35.2 days after the screening (16). Bongers-Schokking et al. reported in their study that there was no neurodevelopmental difference in the patients with CH whose treatment was initiated with appropriate dose in the first 13 days compared to healthy group (17). In our country, the screening program has been implemented for 12 years whereas we have not achived the ideal time for diagnosis although the duration for the diagnosis of CH was reduced.

The mean TSH level was 79.5±59 µIU/mL in patients diagnosed as a result of initial evaluation and 8.15±3.15 µIU/mL in patients diagnosed at follow up in our study. The mean TSH level was found as 55.2±33.85 µIU/mL in the study of Peltek Kendirci et al., 15.8±28.69 µIU/mL in the study of Kor et al. (8,11).

In our study, the rate of presence of symptoms was 36.5% in patients with CH and the most common symptoms were constipation and prolonged jaundice. The rate of presence of concomitant congenital abnormality in patients with CH was found to be 18.3% (11/60). The most common abnormalities were cardiac malformations detected in 7 cases (ASD, VSD, PS, PDA). Three patients were diagnosed with Down syndrome (diagnosed with CH at follow). In the study of Razavi et al., the rate of accompanying abnormality was found to be 19.1% (30/157); 4.6% of abnormalities was cardiac malformations and the rate of down syndrome was 7.6% (12/157) (18).

In our study, 16 patients (33.3%) with CH were diagnosed as dysgenesis. Hyperplasia was detected in 16 patients with a diagnosis of **dyshormonogenesis** was 33.3%. The majority of cases with normal thyroid gland will be diagnosed with transient hypothyroidism but some of them may be diagnosed with thyroid **dyshormonogenesis** so that it was concluded that the exact ratio can only be given when the patients reached 3 years old and attempted to discontinue the drug. Kor et al. reported that the etiological distrubition of CH was evaluated by thyroid USG and thyroid dysgenesis rate was found to be 28.2% of patients (24% hypoplasia, 4% agenesis), 71% of patients were found to be normal thyroid gland and 0.4% of patients were found to have hyperplasia (8). In the study of Kusdal et al., 28.2% of patients had thyroid dysgenesis (10.2% agenesis, 10.2% hypoplasia, 5.2% ectopia, 2.6% hemiagenesis) and all the remaining cases had normal thyroid gland by ultrasonographic evaluation (14). Ozgelen et al. repoted that rate of dysgenesis was found to be 83.7% of the patients with CH (51.7% hypoplasia, 21.7% agenesis, 10.3% ectopia) and rate of dyshormonogenesis was found to be 10.3% in patients; etiological distribution in this study was made only among the cases with permanent CH (13). Similarly, in the study of Bezen et al., etiological distribution was evaluated among the cases with permanent CH; rate of dysgenesis was found to be 52.2% (34.8% hypoplasia, 17.4% ectopia) and rate of **dyshormonogenesis** was found to be 47.8% in patients (19). Although there are more studies in the literature reported that the rate of dysgenesis is high (20,21); there is an increase in the rate of **dyshormonegenesis** in recent studies in accordance with our study (19,22). In the study conducted by Olivieri et al., the rate of dysgenesis in CH cases was found to be 82% between years 1987 and 1998; it was reported that it was decreased significantly compared to the previous period with a rate of 58% between years 1999 and 2006. In the second period of the study, it was stated that the rate of detection of normal and hyperplastic thyroid gland increased compared to the first period; in addition, it was emphasized that the rate of dyshormonogenesis was significantly higher in patients who had parenteral consanguinity (23). The consanguinity rate in our study was higher in patients with CH but there was no difference in consanguinity rate according to the etiology of CH. In the group of dysgenesis, while consanguinity rate was 41.2%, it was 50% in the non-dysgenesis group (25% in the cases with normal thyroid gland and 25% in the cases with hyperplasia). However, we think that the exact effect of consangunity in etiological distrubion in CH may be remarked by the evaluation of patients with persistent CH at follow up.

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Table 1. Clinical features in all cases

	Total (n=109)	CH+ (n=60)	CH- (n=49)	CH+/CH- p value
Gender **Female** **Male**	 49 (45%) 60 (55%)	 29 (48.3%) 31 (51.7%)	 20(40.8%) 29(59.2%)	0.433
Birth Week	38.07±2.30	38.3±1.65	37.6±2.88	0.215
Maturity **Term** **Preterm**	 92(84.4%) 17(15.6%)	 51 (85%) 9 (15%)	 41(83.7%) 8(16.3%)	0.850
Type of Delivery **Vaginal** **C/S**	 53(48.6%) 56(51.4%)	 30(50%) 30(5%)	 23(46%) 26(54%)	0.750
Birth weight (gram)	3042.06±593.2	3064.3±510.47	3014±685	0.751

Table 2. Demographic characteristics of CH group and health group

	CH+ (n=60)	CH- (n=49)	CH+/CH- p value
Consanguinity	19(31.7%)	4(8.16%)	0.004
Thyroid Disease in Family	26(43.3%)	22(44.8%)	0.870
CH in Family	7(11.22%)	5(10.20%)	1.00
Iodized Salt Consumption in Pregnancy	50(83.3%)	34(69.4%)	0.135
Iodine Exposure **Umblical Care** **Other**	11(15.6%) 10(90.9%) 1(9.1%)	6(12.2%) 5(83.3%) 1(16.7%)	0.544

Table 3. Postnatal age, anthropometric measurements and laboratory findings in all cases

	Total (n=109)	CH+ (n=60)	CH- (n=49)	CH+/CH- p value
Postnatal age (day)	27.47±14.2	23.9±13.01	31.8±14.4	<0,001
Weight (gr)	3960±590	3850±800	4100±920	0.058
Height (cm)	52.1±2.42	51.5±1.99	52.9±2.68	0.052
Head Circumference (cm)	36.3±1.87	35.9±1.66	36.9±1.99	0.053
TSH (µIU/mL)	42.2±54.3	71.05±59.2	6.95±4.49	<0.001
fT4 (ng/dL) **low** **normal**	1.04±0.37 33(30.2%) 27(69.8%)	0.83±0,35 33(55%) 27(45%)	1.30±0.17 - 49(100%)	<0.001
fT3 (pg/mL)	3.79±0.93	3.44±1.03	4.2±0.56	0.001