Congenital hypothyroidism screening program in Turkey: a local evaluation

Yusuf Kuşdal, Gül Yeşiltepe-Mutlu, Elif Özsu, Filiz Mine Çizmecioğlu, Şükrü Hatun

Pediatric Endocrinology and Diabetes Unit, Department of Pediatrics, Kocaeli University Faculty of Medicine, Kocaeli, Turkey. E-mail: sukruhatun@gmail.com

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It was aimed to evaluate the national congenital hypothyroidism program in terms of thyroid-stimulating hormone (TSH) cut-off level, frequency of cases that required treatment and the stages before treatment in the Kocaeli district area. This research was performed with the contribution of Kocaeli University Medical Faculty, Pediatric Endocrinology Department, and the Kocaeli Local Health District. 25,188 babies born in 2009 were evaluated. The previous laboratory data including heel prick samples and venous thyroid function tests (TSH, free/total T4 levels) of babies requiring investigation were evaluated retrospectively. 49,785 heel prick blood samples were collected from 25,188 babies born in our region. TSH levels of 3,355 babies in the first sampling were greater than the cut-off level (15 mIU/L) (recall rate was 13.3%). Venous sampling was required for 107 babies, and 39 of them needed to be treated (treatment rate was 1/645). Eleven of the babies who were treated were diagnosed with thyroid dysgenesis. Families of the babies who needed further venous sampling were given final results in an average of 28.5 days after the first heel sampling. We concluded that the recall rate is high, but raising the cut-off level for TSH may lead to overlooking the diagnosis of thyroid dysgenesis. The duration for providing final results to the families is quite long. It is necessary to take venous blood samples in the pediatric endocrinology units to reduce this duration.

Key words: congenital hypothyroidism, screening, thyroid-stimulating hormone cut-off level.

Congenital hypothyroidism (CH) is one of the most important causes of preventable mental retardation. The goals of neonatal CH screening programs are early diagnosis and treatment. Although the CH screening programs were implemented 30 years ago, the optimal screening methods and cut-off levels for thyroid-stimulating hormone (TSH) remain controversial (1). The CH screening program in Turkey has been performed since 2006. Initially, the cut-off level for TSH was 20 mIU/L, but it was lowered to 15 mIU/L in recent years (2). In the present study, the local results of the national CH screening program were evaluated in terms of TSH cut-off level and frequency of cases that required treatment, along with stages before treatment.

Material and Methods

National Congenital Hypothyroidism Screening Program Protocol and Subjects

As part of the National Congenital Hypothyroidism (CH) Screening Program nationwide, capillary blood sample by heel prick is taken from all babies between the 3rd-5th days or prior to discharge from early discharged babies born in health facilities. This program is based on primary TSH measurements. The TSH cut-off level is 15 mIU/L. Infants with TSH level of 15-50 mIU/L are recalled for a second sampling. Infants with TSH level >50 mIU/L in the first heel prick and TSH >15 mIU/L in the second heel prick are evaluated with venous TSH and T4 measurements.

Table I. TSH Levels of Patients with First Heel TSH Level >15 mIU/L

TSH level (mIU/L)	n	Percent (%)
15-20	2024	60.3
20-30	1033	30.8
30-50	263	7.8
>50	35	1.1
Total	3355	100

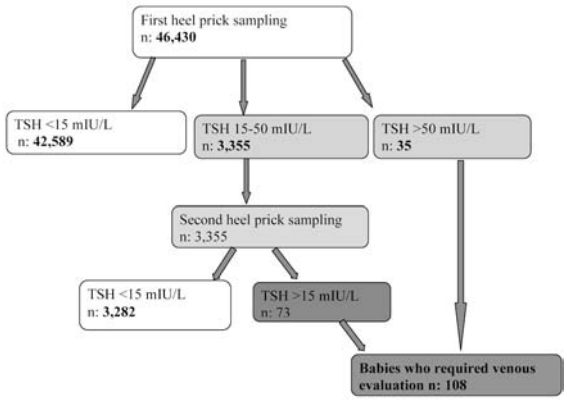

Figure 1. CH screening program flow chart.

In 2009, 25,188 babies were born in Kocaeli, and 49,785 heel pricks (including new, inappropriate and second samples) were performed in these babies. TSH levels were <15 mIU/L in 42,589 samples, 15-50 mIU/L in 3,355 samples and >50 mIU/L in 35 samples. TSH levels were >15 mIU/L in the second heel pricks of 73 babies. One hundred and eight babies in total (35 and 73 babies according to first and second heel pricks, respectively) were recalled for venous sampling (Fig. 1). We could contact only 89 of these patients in this study. Thyroid function tests of the patients, requirement of treatment and the period prior to the initiation of treatment were evaluated retrospectively.

Laboratory Methods - Image Studies

MicroELISA method is used for capillary blood TSH measurement in CH screening central laboratories. Venous TSH and T4 levels are assayed by ADVIA Centaur (Siemens, Healthcare Diagnostics Inc, Tarrytown, NY, USA), with chemiluminometric detection. Reference ranges for children born at term for TSH, FT4 and T4 are 0.7-9.3 mIU/L, 8.5-28.4 pmol/L and 6.5–16.3 g/dl, respectively[3,4]. Neonates with persistent serum TSH ≥10 mIU/L and normal or low T4[5] are considered hypothyroid, and treatment is started. Thyroid ultrasound is performed for babies requiring treatment. Thyroid volume is calculated using the formula {(AXBXC)/1000+(AXBXC)/1000} X 0.523[6]. Thyroid scintiscan is performed for babies with venous TSH level >30 mIU/L.

Statistical Analysis

The data was analyzed with the Statistical Package for the Social Sciences (SPSS) statistics program. Descriptive statistics (mean, standard deviation), t-test and Mann-Whitney U test were used. $p<0.05$ was accepted as significant.

Ethical Aspects

The study was approved by the local Research and Ethics Committee of Kocaeli Local Health Authority. Written informed consent was obtained from parents.

Results

In this study, 49,785 heel prick blood samples were taken from 25,188 babies born in our region (1.97 samples for each baby). TSH levels of 3,355 babies in the first sampling were greater than the cut-off level (15 mIU/L). The average recall rate was 13.3% (TSH levels of patients whose first heel TSH level was >15 mIU/L are given in Table I). Venous blood sampling was required for 108 babies. We were able to contact only 89 of the babies who needed venous evaluation. Some families had moved away from Kocaeli and others had changed their address.

The duration between the first heel prick and recall time was 17.5±9.8 days (1-49 days, median: 17 days). This period was longer than 4 weeks for 11 infants. The families of infants who needed venous evaluation were called on day 21.1±9.5 (4-51 days, median: 21 days), and they admitted to health facilities on day 22.6±9.8 (4-51 days, median: 22 days) for

Table II. Duration for Evaluation

Interval between first heel sampling and recall time for second heel sampling (days)	17.5±9.8 (1-49, median: 17 days)
Age of recall for venous sampling (days)	21.1±9.5 days (4-50, median: 21 days)
Age of admission for venous sampling (days)	22.6±9.8 days (4-5, median: 22 days)
Interval between birth and commencement of venous samplings (days)	30.5±37.6 days (median: 25 days)
Interval between first sample and starting treatment (days)	35.6±58.6 days (median: 21 days)

Table III. Characteristics of Patients Needing Treatment

n	35
Age when treatment started (days)	38.1±58 (4-342 days)
Gender (girl/boy) (percent)	51/49
Mean birth weight (g)	3115±496 (1370-4200) (g)
Mean TSH level in first heel sampling (mIU/L)	39.8±31.9 (15.1-105)
Patients with first heel sampling TSH >15 mIU/L	n: 35 (100%)
Patients with first heel sampling TSH >20 mIU/L	n: 22 (63%)
Mean venous TSH level (mIU/L)	127.2±215 (10-1000)
Mean venous total T4 level (μg/dl)	6.9±4.3 (0.84-17.2)
Mean thyroid volume in ultrasound (cc)	1.26±1.40 (0.31–6.20)
L-thyroxine dosage (μg/day)	35.6±18.5 (6.25-100)

Table IV. Comparison of TSH Cut-Off Levels for Recalling

	1st heel sample TSH>15 mIU/L	1st heel sample TSH>20 mIU/L
n	3355	1331
Recall rate	13.3%	5.2%
Cases needing treatment	35	22
Cases who would be missed		13 (2 cases with thyroid dysgenesis)

venous sampling. The duration prior to venous evaluation is given in Table II.

L-thyroxine treatment was started for 39 babies who required venous evaluation. The incidence of treated infants was 1/649. Eleven babies had thyroid dysgenesis (4 with thyroid agenesis, 4 with hypoplastic thyroid gland, 2 with ectopic thyroid gland, and 1 with hemiagenesis). The incidence of thyroid dysgenesis was 1/2500 livebirths. The remaining 24 patients were the babies with normal thyroid ultrasound, but impaired thyroid function tests. The characteristics of patients who needed treatment are given in Table III.

The cut-off level for TSH is 15 mIU/L in our national CH screening program, but if the cut-off level for investigation of CH was 20 mIU/L, 1,331 babies would be recalled for a second heel sampling (recall rate would be decreased to 5.2%); however, 13 cases eventually requiring thyroxine treatment would be missed. The comparison of TSH cut-off levels for recalling is given in Table IV. The mean TSH level in the first heel prick of the cases whose 1st heel sample was 15-20 mIU/L was 17.09±1.37 mIU/L (15.1-19.3, median: 16.8). The mean TSH level in the second heel prick, the mean TSH level and total T4 in the venous blood were 35.5 ± 30.4 (15.8-105, median: 25.9)

Table V. Characteristics of the Na-L-Thyroxine-Supplemented Patients with TSH Level of 15-20 mIU/L in the First Heel Prick

Case	1st heel prick TSH (mIU/L)	2nd heel prick TSH (mIU/L)	Venous TSH (mIU/L)	Venous total T4 (μg/dl)	Thyroid volume	Final diagnosis	Follow-up
1	18.1	30	50.89	9.6	Normal	Unknown	Receiving 25 μg/day thyroxine
2	18	26.02	58.18	10.6	Normal	Transient congenital hypothyroidism	Treatment stopped
3	19.3	21.3	52.77	8.6	Normal	Transient congenital hypothyroidism	Treatment stopped
4	17.7	105	268.3	1.4	Increased	Dyshormonogenesis	Receiving 50 μg day thyroxine
5	15.2	38.8	65.17	4	Normal	Transient congenital hypothyroidism	Treatment stopped
6	15.9	25.9	25.18	7.1	Normal	Transient congenital hypothyroidism	Treatment stopped
7	18.7	16.3	29.26	11.3	Normal	Unknown	Receiving 37.5 μg/day thyroxine
8	16.8	15.9	43.67	10.4	Normal	Transient congenital hypothyroidism	Treatment stopped
9	16.7	16.5	72	8.9	Normal	Unknown	Unknown
10	18.4	34.2	141.3	3.7	Hemiagenesis	Dysgenesis	Receiving 37.5 μg/day thyroxine
11	15.8	17.4	50.76	6	Normal	Unknown	Receiving 37.5 μg/day thyroxine
12	15.1	98.9	131.7	2.5	Increased	Dyshormonogenesis	Receiving 25 μg/day thyroxine
13	16.5	15.8	37.42	2.5	Normal	Transient congenital hypothyroidism	Treatment stopped

mIU/L, 78.9±66.9 (25.1-268.3, median: 52.7) mIU/L, and 6.6±3.5 (1.4-11.3, median: 7.1) μg/dl, respectively. The final diagnosis of six cases was transient CH, and their treatment was stopped at the age of 3 years. In 4 cases, the final diagnosis was unknown (whether it was permanent or transient CH), because they were under 3 years of age and interruption of the treatment was not tried. The characteristics of the Na-L-thyroxine-supplemented patients whose TSH level was 15-20 mIU/L in the first heel prick are given in Table V.

Discussion

The congenital hypothyroidism (CH) screening program has been implemented in Turkey since 2006. It is based on TSH measurement by heel prick between the 3rd and 5th days of life. In practice, however, in most hospitals in our region, heel pricks are taken in the first 48 hours from the babies who are discharged early, and this causes the false-positive results and high recall rate. Two heel pricks are taken per baby in our area within the scope of the CH screening program, increasing the costs.

The high rate of false-positive results with the classic cut-off TSH levels (20-25 mU/L) is due to the normal increase in TSH postnatally[5]. It was shown that normal TSH values in the first 24 hours of life are usually less than the cut-off level of 20-25 mU/L[7,8]. Allen et al.[9] indicated that in the event of using age-adjusted TSH cut-offs, a 50% reduction in abnormal values occurred. Thus, the high cost due to recurrent heel pricks for babies discharged early may be prevented by using age-adjusted cut-off levels[1,5].

The most important goals of CH screening programs are early diagnosis and treatment of CH. Preferably, the diagnosis must be confirmed within the first 14 days, and treatment must be started[10]. There are also some studies emphasizing the necessity of starting the treatment no later than three months (ideally 1 month) after the first sample[11]. In our study, the mean age of the patients who were treated was 38 days, and the mean duration between the first heel prick and the initiation of the treatment was 35 days. Although these numbers are acceptable, earlier treatment schedules were noticed in other studies from different countries. Time to start treatment was 8.5 days in Bahrain, 9-46 days in Lebanon and 12.5 days in Chile, respectively[12-14]. In our region, the institutions where venous blood is collected are separate from those where the venous thyroid functions are evaluated. Therefore, there is a delay in starting treatment. We suggest that if venous blood sampling and evaluation of thyroid functions are performed in the same health institution, this delay can be prevented.

The frequency of permanent CH is variable in different countries. It was reported that the prevalence of CH in the Greek Cypriot population between 1990-2000 was 1/1800[15]. The results of the screening program for CH in Italy noted the incidence of CH as 1/1446 between 1999-2005[16]. Nonetheless, CH is more common in Eastern countries, for example, the incidence of permanent CH was found as 1/748 in Iran between 2002-2005[17]. CH incidence before the CH screening program in Turkey was reported as 1/2736-1/2326[18,19]. A study from Konya noted that the CH incidence between 1999-2007 was 1/2183[20]. Our study revealed that 1/645 (thyroid dysgenesis 1/2500) babies born in 2009 in our region needed L-thyroxine treatment. These cases were treated according to the CH screening program algorithm, regardless of having permanent or transient CH. The high frequency of L-thyroxine treatment requirement may result from the probable transient CH cases. These cases are still followed; however, the discontinuation of treatment has not been tried because of the short observational period. The relatively short observational period might be considered a limitation of this study. It is planned to reevaluate these patients at three years of age in terms of stopping the treatment. In babies with markedly decreasing Na-L-thyroxine requirement, treatment may be stopped earlier than three years of age.

Variable TSH cut-off levels have been used in CH screening programs worldwide. The variability of these levels affects the false-positivity and false-negativity rates[21]. According to a study published in 2004, the cut-off level for TSH ranged between 5-25 mIU/L in European countries[22]. As might be expected, the recall rate and CH frequency were higher in the countries that used lower cut-off levels[22]. It was reported that there was a two-fold increase in CH incidence in Italy when the TSH cut-off level was decreased from 20 mIU/L to 10-12 mIU/L[16]. Similarly, permanent CH incidence had increased from 1/3384 to 1/1749 in Greece, concurrent with the decrease in TSH cut-off level from 20 mIU/L to 10 mIU/L. One-third of the patients with permanent CH were found to have neonatal TSH levels between 10-20 mIU/L in the same study. In other words, if the cut-off level was 20 mIU/L, one-third of the cases with permanent CH would be missed[23]. A study from our country, in which the TSH cut-off level was taken as 20 mIU/L (before the CH screening program started), the recall rate was reported to be 1.6%[18]. Regarding the cut-off level for TSH of 15 mIU/L, we determined the recall rate to be 13.3% in our region. If the cut-off level was 20 mIU/L, the recall rate would decrease to 5.2%, but 13 cases who need to be treated would be missed. Of the three cases with very high venous TSH levels, two of them were diagnosed with dyshormonogenesis and one with thyroid dysgenesis. It is obvious that their developmental scores would be negatively affected if they were not diagnosed and treated immediately. However, 6 of these 13 cases were diagnosed with transient CH, and their treatment was stopped.

In conclusion, lowering the cut-off level will probably increase the cost of the screening program; however, the number of the missed cases due to high cut-off levels is substantial. Taking two samples (before discharge and in the 2nd week) for CH screening may increase the recall rate and cost of the national CH screening program; therefore, age-adjusted TSH cut-off levels may be used for babies discharged early. Also noteworthy is the duration for reporting final results to the families. Venous blood sampling in Pediatric Endocrinology Units may reduce this waiting period.

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