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The evaluation of transient hypothyroidism in patients diagnosed with congenital hypothyroidism

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Background/aim: Congenital hypothyroidism (CH) is divided into two groups as 'permanent' and 'transient'. We aimed to determine the rate of transient and permanent congenital hypothyroidism of the newborns referred to our clinic.

Materials and methods: Of the newborns who were referred to our clinic from the neonatal screening program, those who were diagnosed with CH and started treatment were included in the study. The treatments of the patients whose required daily treatment dose was reduced to under 1 µg/kg were terminated and those who were followed monthly and whose fT_4 and thyroid-stimulating hormone (TSH) levels were normal at least 3 times without treatment were considered to have transient hypothyroidism.

Results: Of the 256 newborns referred to our clinic from the neonatal screening program, 114 (44.5%) were diagnosed with CH. Of the CH patients, 70% (n = 58) were evaluated to have permanent and 30% (n = 25) transient hypothyroidism. Neonatal and serum TSH levels and treatment doses were found to be significantly lower in the transient hypothyroidism patients.

Conclusion: Initial measurements of the serum TSH level and the required doses of L-thyroxine therapy for maintaining normal thyroid hormone levels, growth, and development may have a predictive role for differentiating permanent forms of CH from transient forms.

Key words: Thyroid, congenital hypothyroidism, transient, permanent

1. Introduction

Congenital hypothyroidism (CH) is a disease where screening is essential as the disorder is the most common cause of preventable mental retardation; neurological problems can be prevented with early diagnosis and treatment; treatment is inexpensive, easy, and effective; and there is no disease-specific clinical finding in more than 95% of the sick babies in the neonatal period. CH was included in the neonatal screening program in Turkey approximately 7 years ago. Although multiple methods are in use globally, the most common one, as in Turkey, is thyroid-stimulating hormone (TSH) measurement from a blood sample taken from the heel in the first week of life (between days 3 and 7). Congenital hypothyroidism is divided into two main groups as 'permanent' and 'transient'. The deficiency of thyroid hormone production in permanent CH continues throughout life and requires continuous treatment. Approximately 85% of permanent CH cases are sporadic (the most common reason is thyroid dysgenesis) and 15% are hereditary (mostly congenital disorders of thyroid hormone synthesis). A transient deficiency is detected in the thyroid hormones

at birth in transient CH, but typically normal thyroid hormone production occurs in the first months or years of life. Maternal and/or neonatal iodine deficiency or iodine overload, maternal antithyroid drug use in pregnancy, transplacental passage of TSH receptor blocker antibodies, congenital hepatic hemangioma/hemangioendothelioma, and heterozygous mutations in the *THOX2* or *DUOXA2* genes can cause transient CH (1). Diagnosis of transient hypothyroidism is important to avoid lifelong unnecessary therapy with its possible side effects. The financial burden for this unnecessary therapy could also be invested in other health care services (2).

We aimed to determine the rate of transient and permanent CH of the newborns referred to our clinic with a preliminary diagnosis of CH from the neonatal screening program in this study.

2. Materials and methods

Children diagnosed with congenital hypothyroidism who started treatment among the newborn babies who were referred to the Dr. Sami Ulus Women and Children's Health Training and Research Hospital Pediatric Endocrinology

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Clinic between May 2009 and August 2011 from the neonatal screening program due to TSH elevation were included in the study. The data of the patients recorded in the hospital's information administration system were retrospectively analyzed.

TSH measurement in capillary whole blood taken after postnatal day 3 is used for neonatal hypothyroidism screening in Turkey. The TSH cut-off level was 15 mIU/L between May 2009 and August 2011. Babies with a capillary blood TSH level between 15 and 50 mIU/L were recalled for repeat TSH measurement and the serum TSH and free T_4 (fT_4) levels of the babies whose TSH level in the repeated sample was over 15 mIU/L or whose TSH level in the first capillary blood sample was over 50 mIU/L were measured. Of the babies found to have serum fT_4 decrease or TSH elevation and referred to our clinic, patients with a TSH level over 10 mIU/L and fT_4 level at the lower normal limit or below were diagnosed with 'primary CH' and were started to be treated with L-thyroxine at a daily dose of 8–15 $\mu\text{g}/\text{kg}$ by taking their fT_4 levels into account. The L-thyroxine dose may be increased or decreased based on the normalization of the T_4 /TSH levels. Infant diagnosed with CH were followed every month for the first year and every 2–3 months thereafter. The birth weight, time of birth (prematurity status), neonatal screening day, application date, neonatal TSH, serum TSH, total T_4 (TT_4), fT_4 levels, treatment initiation age, follow-up period, transient hypothyroidism treatment stoppage time, drug dose at time of discontinuation, and duration of follow-up after treatment discontinuation of the patients diagnosed with CH were evaluated. Sonographic evaluation of the thyroid gland (thyroid USG) was performed and the etiology was evaluated. The transverse (T), anteroposterior (AP), and sagittal (S) lengths of the thyroid gland lobes were measured and each lobe volume was calculated separately ($T \times AP \times S \times \pi/6$). The lobe volumes were added without including the isthmus to find the thyroid volume. The thyroid was considered to have normal volume when the volume was between 0.44 and 1.5 mL, hypoplastic when ≤ 0.44 mL, and hyperplastic when ≥ 1.5 mL (3). Excluding those who were known to have permanent hypothyroidism, patients with a normal clinical and laboratory course whose daily required treatment dose fell under 1 $\mu\text{g}/\text{kg}$ and whose treatment was terminated, who continued monthly follow-up, and whose fT_4 and TSH levels were normal at least 3 times without treatment were considered to have 'transient hypothyroidism'. The clinical and laboratory findings of the transient and permanent hypothyroidism patients at admission and during follow-up were compared.

Thyroid function tests were performed at the biochemistry laboratory of our hospital by using the immune chemiluminescence method with an Advia Centaur device. The normal range was 0.8–5.4 $\mu\text{IU}/\text{mL}$ for TSH and 0.9–2.1 ng/dL for fT_4 (4).

2.1. Statistical analyses

SPSS 16.0 was used for statistical analyses. The Kolmogorov–Smirnov test was used to determine normal distribution. Descriptive statistics were presented as mean \pm standard deviation (SD) for normally distributed data and as counts and percentages for categorical data. The relationship between the categorical variables was examined using the chi-square test. Student's t-test was used for the comparison of two groups with normally distributed variables, and the Mann–Whitney U test was used for data not normally distributed. Results were evaluated with a confidence interval of 95%, and $P < 0.05$ was considered statistically significant.

3. Results

We diagnosed CH in 114 of 256 newborns who were referred to our clinic from neonatal screening programs (44.5%) (Table 1). Of these patients, 58.7% ($n = 67$) came from Afyonkarahisar, 22.8% ($n = 26$) from Ankara, and 18.5% ($n = 21$) from provinces neighboring Ankara.

The mean birth weight of patients with CH was 3230 ± 486 g (2140–4500). Three of these patients (2.6%) had a history of premature birth and 3 patients (2.6%) had a history of maternal antithyroid drug use. Girls made up 55.3% of the patients ($n = 63$). The mean thyroid volume of the 105 patients whose thyroid imaging was performed was 0.86 ± 0.49 (0.17–2.2) mL with 13.3% ($n = 14$) of the patients found to have hypoplasia, 6.6% ($n = 7$) agenesis, 1.9% ($n = 2$) ectopia, and 10.4% ($n = 11$) hyperplasia. A normal thyroid was present on USG in 67.6% of the patients ($n = 71$).

Of the patients who were followed with a diagnosis of CH, 27.2% ($n = 31$) did not attend regular follow-up appointments. Therefore, evaluations were performed in the 83 cases that could be followed. Of the CH patients, 70% ($n = 58$) were evaluated as having permanent and 30% ($n = 25$) as having transient hypothyroidism. The patients with CH were treated for 18.1 ± 11.5 (2.0–43.0) months and were followed for an additional 14.8 ± 8.0 (3.0–36) months after the termination of their treatments. One patient whose treatment was terminated had to start treatment again.

The male/female ratio was 1.08 in patients with transient hypothyroidism and 1.5 in those with permanent hypothyroidism. No statistical difference was found between the groups in terms of sex distribution ($P = 0.322$). There was no difference between the birth weight, days of screening and application, serum fT_4 and TT_4 levels, thyroid volume, and treatment start time in comparison of the findings of patients with permanent and transient hypothyroidism, whereas the neonatal and serum TSH levels in the transient hypothyroidism group were significantly lower. L-thyroxine doses were found to

Table 1. The characteristics of hypothyroidism patients at admission.

| | Mean \pm SD | Min-max |
|---|------------------|------------|
| Birth weight (g) | 3230 \pm 486 | 2140-4500 |
| Day of application | 21.3 \pm 10.2 | 4.0-75.0 |
| Day of screening | 8.44 \pm 5.93 | 1.0-25.0 |
| Neonatal TSH (μ IU/mL) | 48.1 \pm 28.3 | 15.1-111.8 |
| Serum TSH (μ IU/mL) | 55.2 \pm 33.85 | 10.7-150.0 |
| Serum TT ₄ (μ g/dL) | 6.42 \pm 2.98 | 1.00-13.4 |
| Serum fT ₄ (ng/dL) | 0.82 \pm 0.42 | 0.3-2.1 |
| Thyroid volume (mm ³) | 0.86 \pm 0.49 | 0.17-2.2 |
| Time of the treatment initiation (day) | 19.7 \pm 8.30 | 5-60 |
| Treatment duration (months) | 24.7 \pm 12.9 | 2-50 |
| Treatment dose (μ g kg ⁻¹ day ⁻¹) | 2.29 \pm 1.33 | 0.9-8.25 |
| Follow-up duration (months) | 27.7 \pm 12.9 | 3-51 |

be significantly higher in the permanent CH group (Table 2). All the patients with a history of maternal antithyroid drug use were found to have transient CH. A history of premature birth was present in 3.4% (n = 2) of the patients with permanent CH and 4% (n = 1) of the patients with transient CH.

4. Discussion

We found that 44.5% of newborns were found to have TSH elevation in the neonatal screening program and were referred to our clinic with CH. Among the CH group, 30% had transient CH in this study. Excluding those who were known to have permanent hypothyroidism, patients with a normal clinical and laboratory course whose daily required treatment dose fell under 1 μ g/kg and whose treatment was terminated, and the patients on monthly follow-up whose fT₄ and TSH levels were normal at least 3 times without treatment, were considered to have transient hypothyroidism in our study. The definition of transient hypothyroidism in the medical literature is variable. Different descriptions are used even in different parts of the same country. There are therefore likely to be significant differences between the reported incidence rates of transient hypothyroidism depending on its definition (2). Treatment of children with CH, excluding those known to have thyroid dysgenesis, is usually terminated around the age of 3 in the literature and those who do not require drug treatment afterwards are considered to have experienced transient CH. Studies from other parts of the world that use this description have reported the incidence of transient hypothyroidism in children with CH as 1%-

50%. It is generally accepted that 10-15% of primary CH patients are diagnosed with the transient type (5). The transient CH rate was 38% in France (6) and 38.1% in Italy (7). The same rate was 46.4% and 40.2% in two different studies conducted in Iran (8,9). In addition to these rates that are higher than those in our study, lower transient CH rates such as 17.7% in Egypt (5) and 8.3% in Saudi Arabia (10) have also been reported. The transient CH rate in the United States has been reported as 28%, similar to our results (11,12). These variations in incidence may be due to different environmental, genetic, and immunological factors as well as ethnicity. A study from İstanbul studied 182 patients and found 54 (35.7%) patients with transient hypothyroidism, 97 (64.3%) with permanent CH, and 31 patients with isolated hyperthyrotropinemia (13). The transient CH rate was 23.7% in a study conducted in İzmir (14). Of the patients in our study, 58.7% (n = 67) came from Afyonkarahisar in the Aegean region where the studies of Ünüvar et al. were conducted (14), but the rest were from Ankara and neighboring provinces. The reason for the difference in the rate of transient CH may be due to the environment where the patients lived.

The different etiology of transient CH between regions may also cause differences in incidence. Transient CH may be due to maternal factors such as iodine deficiency, excessive iodine intake, antithyroid medication, or presence of antibodies against thyroid tissue during pregnancy. Very low birth weight (<1500 g), prematurity (<37 weeks gestation), immaturity of thyroidal iodine organification, exposure to excess iodine (e.g., use of iodinated disinfectants or contrast agents), and gene

Table 2. The characteristics of patient groups with transient and permanent hypothyroidism, mean \pm SD (min–max).

| Characteristics | Permanent hypothyroidism (n = 58) | Transient hypothyroidism (n = 25) | P |
|--|-----------------------------------|-----------------------------------|-------|
| Birth weight (g) | 3233.9 \pm 448.7 (2140–4500) | 3223.9 \pm 574.1 (2390–4500) | 0.935 |
| Day of application | 19.2 \pm 9.1 (6.0–64.0) | 21.5 \pm 9.08 (4.0–43.0) | 0.828 |
| Day of screening | 6.7 \pm 5.7 (1.0–22.0) | 9.8 \pm 5.6 (1.0–21.0) | 0.762 |
| Neonatal TSH (μ IU/mL) | 52.4 \pm 31.2 (15.1–111.8) | 38.4 \pm 20.5 (15.2–98.0) | 0.002 |
| Serum TSH (μ IU/mL) | 60.7 \pm 37.1 (10.7–150) | 42.5 \pm 18.3 (19.7–75) | 0.002 |
| Serum TT ₄ (μ g/dL) | 6.2 \pm 2.9 (1.0–12.7) | 7.3 \pm 2.7 (2.0–12.3) | 0.464 |
| Serum fT ₄ (ng/dL) | 0.7 \pm 0.3 (0.3–2.2) | 0.7 \pm 0.2 (0.3–1.3) | 0.139 |
| Thyroid volume (mm ³) | 0.8 \pm 0.5 (0.1–2.2) | 0.9 \pm 0.4 (0.5–1.2) | 0.558 |
| Time of the treatment initiation (day) | 18.9 \pm 7.7 (6.0–47.0) | 21.8 \pm 8.0 (10.0–43.0) | 0.860 |
| Treatment duration (months) | 29.2 \pm 11.0 (3.0–50.0) | 18.1 \pm 11.5 (2.0–43.0) | 0.842 |
| Treatment dose (μ g kg ⁻¹ day ⁻¹)* | 2.2 \pm 1.3 (0.9–8.2) | 0.6 \pm 0.3 (0.6–0.9) | 0.004 |
| Follow up duration (months) | 29.5 \pm 11.1 (3.0–51.0) | 32.5 \pm 11.1 (12–50) | 0.921 |

*This is the dose at final follow-up for patients with permanent hypothyroidism and the dose at discontinuation of treatment in patients with transient hypothyroidism.

mutation may also contribute to transient CH. The reason for the hypothyroidism cannot be determined in some cases (9,15–17). A history of maternal antithyroid drug use was present in 2.6% (n = 3) of our patients and all were diagnosed to have transient CH. A history of premature birth was present in 3.4% of the patients with permanent CH (n = 2) and 4% of the patients with transient CH (n = 1). On a global basis, iodine deficiency is the most common cause of transient hypothyroidism (5). Although the use of iodized salt has become mandatory in Turkey since the initiation of the national program in 1998, studies have shown that the rate of iodine deficiency continues to be significantly high in sensitive populations such as pregnant women and nursing mothers (18). In addition, iodine deficiency has also been found at a rate of 41.9% in school children (19). The maternal and neonatal iodine statuses and whether antibodies against thyroid tissue were present were not known in our study. These are limitations of our study.

The reported female-to-male sex ratio among infants with true CH was 2:1 in studies of European, Australian, and Canadian newborns. The ratio was even higher (2.4:1.0) among newborns with CH caused specifically by thyroid aplasia or ectopia (2). Studies in Italy reported the female-to-male ratio as 2:1 among newborns with thyroid dysgenesis, which accounted for 75% of all newborns with CH; 1:1 among newborns with CH with eutopic (normally positioned and normal appearing) glands; and 0.5:1.0

among newborns with transient hypothyroidism (20). In a Scottish study, the female to male sex ratio was 2.2:1.0 among 224 newborns with definite CH and 1:1 among 88 newborns with transient hypothyroidism (21). Although we found no statistical difference between patients with transient and permanent CH in terms of sex distribution, the male/female ratio was 1.08 in patients with transient CH and 1.5 in those with permanent CH. Although our rates are not as high as in other studies, we similarly found an increased percentage of female patients in the permanent CH group.

The median neonatal and serum TSH levels before treatment were significantly higher in patients with permanent CH than those with transient CH in our study. Similar findings were reported from Iran by Hashemipour et al. (9) and from India by Nair et al. (22). The median TT₄ and fT₄ levels before starting treatment were not significantly different among patients with permanent and transient CH. This was reported also by Hashemipour et al., while the initial T₄ levels correlated with the etiology of CH in other reports (23). These findings indicate that the first TSH and T₄ levels may have a predictive role for differentiating the permanent forms of CH from the transient forms.

The most common cause of permanent CH is thyroid dysgenesis (1). On the other hand, Gaudino et al. (6) and Lombard et al. (24) reported the frequency of dyshormonogenesis to be higher than that of thyroid

dysgenesis among patients with CH. Thyroid dysgenesis was the cause of permanent CH in 21% of the cases in our study. We think that this difference between the results is associated with the higher frequency of consanguineous marriage in our region, the small patient population, and the presence of undiagnosed CH in the family history.

Several studies in the literature reported permanent CH patients to require higher doses of L-thyroxine for TSH and fT_4 normalization. Similarly, other studies have shown that low-dose L-thyroxine therapy was sufficient for maintaining normal thyroid hormone levels, growth, and development in patients with transient CH (14). The L-thyroxine dose requirement in the permanent CH group was higher than in the transient CH group in our study

and this was consistent with the literature.

In conclusion, the high incidence of transient CH in our study could be explained by iodine deficiency. Initial measurements of serum TSH level and the required doses of L-thyroxine therapy for maintaining normal thyroid hormone levels, growth, and development may have a predictive role for differentiating permanent forms of CH from the transient forms. Diagnosing transient hypothyroidism is important to avoid lifelong unnecessary therapy. Further studies with larger sample sizes and long-term follow-up are needed to confirm the etiology and determine the predictive factors to differentiate forms of CH.

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