Monitoring and prognostic evaluation of patients with congenital hypothyroidism treated in a pediatric endocrinology unit

Tolga Ünüvar[1], Korcan Demir[1], Ayhan Abacı[1], Ali Ataş[1], Atilla Büyükgebiz[2], Ece Böber[1]

Units of Pediatric Endocrinology, Department of Pediatrics, [1]Dokuz Eylül University Faculty of Medicine, İzmir, and [2]Bilim University Faculty of Medicine, İstanbul, Turkey. E-mail: tunuvar@gmail.com

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In this study, the etiological factors, diagnostic approaches, dose, and duration of treatment were compared between cases with transient and permanent congenital hypothyroidism (CH) with respect to prognosis. One hundred and twenty-two patients who received treatments with the diagnosis of CH in the last 10 years were included in the study. The records of the patients were reviewed retrospectively. Serum thyroid- stimulating hormone (TSH) levels at the time of diagnosis were found to be significantly higher, and total thyroxine (TT4) levels were found to be significantly lower in the permanent CH group in comparison to the transient CH group. A statistically significant difference was present between the groups regarding treatment doses, the time needed for TSH decrease to <5 mIU/ml and the TSH and free thyroxine (FT4) levels obtained one month after discontinuation of the treatment. The association between age at the time of initiation of treatment and results of Denver Developmental Test was noted to be statistically significant. The high frequency of transient CH in our region leads to the result that some of the patients had to be unnecessarily treated with L-thyroxine for a long time.

Key words: congenital hypothyroidism, thyroid hormone, transient hypothyroidism.

Congenital hypothyroidism (CH), known since the antiquity, is no longer a social problem owing to the screening programs being employed in developed countries for 30 years. Nevertheless, it still represents a major public health problem and is an important cause of mental retardation in geographical regions characterized by iodine deficiency and in undeveloped countries where screening programs are not yet in place[1-5].

Since delays in the diagnosis and treatment of CH may lead to neurological sequelae including mental retardation, poor motor coordination, ataxia, spastic diplegia, muscular hypotonia, strabismus, learning disorders, and attention deficiency, early diagnosis and treatment are critical in CH[2,3,5].

Approximately 10% of the cases diagnosed with CH during screening programs were confirmed to have a transient condition. Although it is more frequently seen in prematures due to the immaturity of the hypothalamic-pituitary axis, transient congenital hypothyroidism (TCH) may also be observed in healthy term infants as a result of intrauterine maternal anti-thyroid drugs, thyroid-stimulating hormone (TSH)-receptor blocking antibodies, which pass from the mother, heterozygous thyroid oxidase-2, TSH receptor mutations, endemic iodine deficiency, or excessive perinatal exposure to iodine[1-3].

The objectives of this study were:

1)to investigate the etiological distribution (familial history, diagnosis confirmed by ultrasonography and scintigraphy), percentiles,

This work has been carried out in Dokuz Eylül University Faculty of Medicine.

ages at diagnosis, symptoms at presentation, thyroid functions at the time of diagnosis and during subsequent monitoring, and medication doses of patients with CH who presented to our center during the past 10 years before the start of the CH screening program, which was introduced by the Ministry of Health in 2007 in Turkey, and thus to compile the relevant data for our region,

2)to identify those diagnosed with TCH within this population and compare them to the patients with permanent congenital hypothyroidism (PCH) for risk factors, drug doses required for treatment, free thyroxine (FT4), free triiodothyronine (FT3), TSH at baseline and during the monitoring period, thyroid ultrasonography, and thyroid scintigraphy, and

3)to investigate associations of treatment compliance, age, gender, baseline TSH levels, starting doses of treatment, and etiology with mental prognoses (by Wechsler Intelligence Scale for Children-Revised (WISC-R) or Denver neurological measurements), and to reveal the problems during monitoring in patients treated for CH.

Material and Methods

The study enrolled 122 patients (59 males, 63 females) treated in the past 10 years for CH in the Pediatric Health and Diseases Endocrinology Department of the Medical Faculty of Dokuz Eylül University. Of the patients with CH reviewed, 76.3% had PCH and 23.7% had TCH. Distribution of patients with PCH and TCH by etiology is provided in Tables I and II, respectively. The patients in the PCH group had a median age of 1.75 months (range: 0.5-19.5) at the time of presentation, while the median age of the patients in the TCH group was 3.1 months (range: 2.7-3.47). Patients' files were reviewed retrospectively. Age, gestational week, height standard deviation score (SDS), weight SDS, familial history, and symptoms and age at diagnosis were recorded for each patient. Total thyroxine (TT4), total triiodothyronine (TT3), FT4, FT3, and TSH levels measured at baseline and one month, at one, two and three months after treatment start, and at one month after treatment discontinuation were also recorded. The doses the patients received at treatment start and after one, two and three years were calculated. Those who had undergone thyroid ultrasonography and Tc99m scintigraphy were recorded. The results of age-based WISC-R and Denver Intelligence Tests were documented for those for whom these measurements had been performed. Assessments were carried out by a psychologist specialized in pediatric psychiatry. Diagnostic criteria for TCH included normal thyroid function tests and normal physical and mental development following discontinuation of 2-3 years of routine treatment. Patients whose thyroid function tests returned to normal during the monitoring period were also categorized as TCH of the newborn.

Laboratory Investigations

Elecsys reagent kits were used for TSH, FT4, FT3, TT4, and TT3 level measurements. Electrochemiluminescence immunoassay was performed by the "ECLIA" method using Roche Elecsys E170 device. Ranges considered normal were 0.4-5 μIU/ml for TSH, 4.5-10.9 μg/dl for TT4, 0.8-1.9 ng/dl for FT4, 60-181 ng/dl for TT3, and 1.57-4.71 pg/ml for FT3.

Statistical Evaluation

The Statistical Package for the Social Sciences (SPSS) 11.5 package software was used for the statistical analyses of the data. Descriptive and frequency analyses were performed. Variables with non-normal distribution were expressed as median (25-75%) and variables with normal distribution were given as mean ± standard deviation. Chi-square test and Student's t test for data with normal distribution, and otherwise Mann-Whitney U test, were used. Statistical

Table I. Distribution of Patients with Permanent Congenital Hypothyroidism by Etiology

Permanent hypothyroidism	Male (n=45)	Female (n=48)	Total (n=93)
Ectopic thyroid gland	8.9% (4)	27.1% (13)	18.2% (17)
Thyroid agenesis	15.6% (7)	10.4% (5)	12.9% (12)
Thyroid hypoplasia	8.9% (4)	4.2% (2)	6.6% (6)
Dyshormonogenesis	66.7% (30)	58.3% (28)	62.3% (58)

Table II. Distribution of Patients with Transient Congenital Hypothyroidism by Etiology

Transient hypothyroidism	Male (n=14)	Female (n=15)	Total (n=29)
Iodine exposure	28.6% (4)	20% (3)	24.1% (7)
Transient hypothyroxinemia	21.4% (3)	0	10.3% (3)
Isolated hyperthyrotropinemia	14.3% (2)	26.7% (4)	20.6% (6)
Maternal anti-thyroid drug	0	6.7% (1)	3.44% (1)
Prematurity	0	20% (3)	10.3% (3)
Etiology unknown	35.7% (5)	26.7% (4)	31% (9)

significance was set at $p<0.05$.

Results

Median gestational age was 39 weeks (range: 38-40 weeks) for the patients with PCH and 39 weeks (range: 37-40 weeks) for those in the TCH group ($p=0.675$). Of the patients in the PCH group, 45.2% (n=42) presented to our clinic after two months, while diagnosis and treatment of 20.7% (n=6) of the patients with TCH were delayed beyond two months.

The proportion of patients with preexisting symptoms at presentation was 20.4% in the PCH group versus 3.4% in the TCH group, with a statistically significant difference between the two groups ($p=0.041$). The most common symptom at presentation was prolonged jaundice in both groups. Thyroid ultrasonography was normal in 55.9% of the patients with PCH versus in 93.1% in the TCH group, and the difference between the two groups was significant ($p<0.001$). Of the Tc99m scintigraphy analyses performed in the PCH group, 37.5% yielded normal results compared to 95.5% in the TCH group ($p<0.001$). Among the patients in the PCH group, those with dysgenesis and suspected dyshormonogenesis differed significantly in TSH levels at the time of diagnosis ($p=0.01$), while FT4 ($p=0.055$) and FT3 ($p=0.353$) levels did

Table III. Comparison of Patients with Permanent and Transient Congenital Hypothyroidism by Birth Weight, Hormone Levels at the Time of Diagnosis and Treatment Doses

Variable	Permanent hypothyroidism	Transient hypothyroidism	*p* value
Birth weight* (kg)	3.24 (2.97-3.60)	3.1(2.7-3.47)	0.411
TSH level at the time of diagnosis* (μIU/ml)	66 (18-100)	15 (9.01-15.1)	<0.001
FT4 level at the time of diagnosis # (ng/dl)	0.83 ± 0.44	0.93 ± 0.41	0.279
FT3 level at the time of diagnosis # (pg/ml)	3.01±1.55	3.32±1.66	0.577
TT3 level at the time of diagnosis # (ng/dl)	2.06±2.84	3.02±3.04	0.108
TT4 level at the time of diagnosis * (μg/dl)	2.4 (1-6.9)	9.9 (4.5 – 10.9)	0.009
Treatment dose at baseline# (μg/kg/g)	10.13±4.38	6.67±3.97	<0.001
Treatment dose after 1 year # (μg/kg/g)	4.79±2.09	3.46±1.23	0.003
Treatment dose after 2 years# (μg/kg/g)	4.08±1.45	2.28±1.07	<0.001
Treatment dose after 3 years# (μg/kg/g)	3.41±1.47	2.16±1.22	0.002

*: Variables with non-normal distribution were expressed as median (25-75%) percentile, using Mann-Whitney U test.
#: Variables with normal distribution were expressed as mean ± standard deviation, using Student's t test.

Table IV. Denver and WISC-R Intelligence Tests in Permanent and Transient Hypothyroidism

	Permanent hypothyroidism % (n)	Transient hypothyroidism % (n)	*P* value
WISC-R			0.497
Normal	60% (6)	100% (3)	
Impaired	40% (4)	0 (0)	
DENVER			0.645
Normal	76.9% (20)	90% (9)	
Impaired	23.1% (6)	10% (1)	

not vary significantly.

The groups of patients with PCH and TCH did not differ significantly in birth weight (p=0.411). Serum TSH levels measured at the time of diagnosis were significantly higher in the PCH group than in the TCH group, and TT4 levels were significantly lower (p<0.001). There were significant differences between the two groups both in the treatment doses required at baseline and in doses used after 1, 2 and 3 years of therapy (Table III).

The groups of patients with PCH and TCH differed also for the time that TSH levels decreased below 5 mIU/ml following L-thyroxine therapy (30.41±10.52 days for the PCH group vs. 25.29±9.92 days in the TCH group; p=0.004). TSH and FT4 levels measured one month after attempting to discontinue treatment at the age of three differed significantly between the groups (p<0.0001 and p=0.041, respectively).

The patients with PCH and TCH treated in our clinic did not differ significantly in terms of Denver and WISC-R test results (Table IV). Comparison of the age at the beginning of treatment and Denver intelligence test results demonstrated that none of the patients who started treatment before two months had impaired results on the Denver test, whereas the results were affected in all patients who presented later than two months, with a significant difference between the groups (p=0.016) (Table V). Data with relevant impact on the intelligence test results were not noted for other variables.

Discussion

The concept of TCH becomes more prominent with the increasing use of newborn screening tests in our country and worldwide. Gaudino et al.[6] identified PCH in 68% and TCH in 32% of 79 patients with CH in France. Similarly, a study in Turkey found that 30% of 182 patients had TCH[7]. Of the patients with CH treated in our polyclinic, 76.3% had PCH and 23.7% had TCH. Both the rates reported in the literature and determined in our study seem to be higher than the estimated figures. The clinical relevance of this is that patients, being diagnosed with hypothyroidism, are forced to receive avoidable long-term L-thyroxine treatment, which indicates how important it is to differentiate the patients with CH on an etiological basis at the time of diagnosis as soon and as accurately as possible. Lombard et al.[8] emphasized that the most frequent finding in TCH was increased urinary iodine levels. The most common cause in our patients with TCH was increased iodine exposure associated with iodine-containing substances and umbilical care. Urinary iodine levels, however, were not measured, which

Table V. Comparison of the Age at Starting Treatment and Denver Intelligence Test Results

	Time of treatment < 2 months (n)	Time of treatment >2 months (n)	P value
Denver intelligence test			0.016
Normal	29	0	
Impaired	0	7	

was a limitation for our study. Studies similar to ours have determined prematurity as a risk factor for TCH[6,9,10], although we did not identify a significant difference in terms of gestational ages between the PCH and TCH groups.

In geographical regions not characterized by iodine deficiency in the overall population, the most common cause of PCH is known to be thyroid dysgenesis, accounting for approximately 75-85% of the cases[1-3,5]. On the other hand, in studies by Gaudino et al.[6] and Lombard et al.[8], the frequency of dyshormonogenesis was higher than of thyroid dysgenesis among patients with CH. In their analysis of patients with CH in the presence of parental consanguinity, the assessment of patients with PCH presenting to our polyclinic demonstrated that dyshormonogenesis was the most common cause, followed by thyroid dysgenesis. We believe that this difference between the results is associated with the higher frequency of consanguineous marriage in our region, the small patient population or presence of undiagnosed familial history of CH.

In a previous study, the time to start treatment was shorter in patients with PCH compared to those with TCH, although the difference was not statistically significant[11]. In our study, 45.2% of the patients in the PCH group presented to our clinic after two months, while diagnosis and treatment of 20.7% (n=6) of the patients with TCH were delayed beyond two months. Although the difference is not significant, this data alone indicates that CH screening programs are necessary in our country.

Clinical diagnosis of CH is possible in only 5% of the cases during the neonatal period[3]. In light of the results of our study, patients symptomatic at the time of diagnosis may suggest that the onset of the event had been during the intrauterine period, the exposure had an early onset, and the prognosis could be permanent.

In a study with Turkish children, thyroid scintigraphy and thyroid ultrasonography were normal in all 54 patients with TCH[7]. In a study by Kreisner et al.[12], thyroid ultrasonography was normal in all subjects in the TCH group, while abnormal results were noted with thyroid scintigraphy for three of 12 subjects. Of these, two subjects had loss of gland function and one had involvement in the superior section of the gland. In a study from France, TCH was identified in 38% of the newborns with normally localized thyroid gland[6]. A significantly lower numbers of pathologies were identified with thyroid ultrasonography and thyroid scintigraphy in patients with TCH than in those with PCH presenting to our polyclinic. Therefore, normal findings with thyroid ultrasonography and thyroid scintigraphy taken at the time of diagnosis may indicate a higher probability of a transient course for CH. The major challenge in imaging is PCH and patients for whom the imaging demonstrated thyroid glands of normal size, function and localization. More detailed studies are needed on this issue.

Consistent with our findings, Hashemipour et al.[11] found significantly higher TSH levels as measured at the time of diagnosis in patients in the PCH group compared to the TCH group. Although this study did not note a difference in T4 levels, in a study from our country, serum TSH levels were significantly higher, while FT4 levels were significantly lower at the time of diagnosis in the PCH group compared to the TCH group[7]. TSH levels measured at the time of diagnosis were significantly higher and TT4 levels were significantly lower in the PCH group than in the TCH group. Given these results, it should be borne in mind that initial measurements of serum TSH and T4 may be a predictive factor in differentiating PCH from TCH, although there are studies that do not support this.

Several studies in the literature demonstrated that patients with PCH required higher doses of L-thyroxine for TSH and FT4 normalization[11,13,14]. Similarly, other studies have also shown that low-dose L-thyroxine therapy was sufficient for maintaining normal thyroid hormone levels, growth and development in patients with TCH[15,16]. In our study, significant differences were noted between the groups of patients with PCH and TCH both in L-thyroxine therapeutic doses required at the treatment start and in treatment doses after 1, 2 and 3 years of therapy. L-thyroxine dose requirement in the PCH group was higher than in the TCH group, consistent with the literature. Results from all these studies may suggest that the prognosis of hypothyroidism could be

predicted by evaluating the dose of L-thyroxine required to normalize TSH levels in a short period of time. In a study by Gaudino et al.[6], TSH levels following treatment discontinuation were significantly lower in the PCH group, as would be anticipated. In our study, TSH and FT4 levels measured one month after attempting to discontinue treatment at the age of three differed significantly between the groups. In the monitoring of patients with CH, when the intention is to discontinue the drug at the end of three years, serum TSH and FT4 levels should be measured again after one month at the latest for the differential diagnosis. Delaying the measurement beyond one month may compromise the patients in terms of mental prognosis.

Although there are several studies in the literature that demonstrate that TSH levels return to normal after one month of treatment on average, no data on its correlation with TCH could be retrieved[4,13,14,17,18]. Salerno et al.[14] emphasized that the time for increased TSH to normalize was a major indicator of whether mental development would be affected. In our study, the time for TSH levels to decrease below 5 mIU/ml following L-thyroxine therapy was significantly lower in the PCH group than in the TCH group. Although the number of patients was limited, we can conclude based on the data obtained in the present study that the patients whose TSH levels return to normal in less than 30 days have a higher probability for transient type of hypothyroidism.

The study by Yang et al.[15] demonstrated that physical and mental development of patients with TCH during one-year monitoring after discontinuation of treatment at the age of 2-3 was similar to that in healthy children. In a meta-analysis of seven studies, Derksen-Lubsen et al.[19] compared 670 children with CH and 570 controls, and found a reduced IQ score by 6.3 for children with severe CH compared to the control group. Kreisner et al.[20] also demonstrated that baseline T4 levels as well as the mother's educational level and frequency of follow-up visits had effects on cognitive functions. The patients with PCH and TCH treated in our clinic did not differ significantly in terms of Denver and WISC-R test results. This indicates that starting treatment at appropriate doses and close monitoring with frequent visits contribute to normal motor and mental development in patients with PCH.

Many studies in the literature demonstrate a marked improvement in IQ levels in children whose treatments were started within the first two weeks, indicating that the severity of CH may be compensated by early onset of treatment[21-23]. Kempers et al.[24,25], however, reported that the severity of CH rather than the time of starting treatment was more predictive of long-term outcomes in cognitive and motor functions. In our study, comparison of the age at starting treatment and Denver Intelligence Test results demonstrated that none of the patients who started treatment before two months had impaired results with the Denver test, whereas the results were affected in all patients who presented later than two months for any reason, with a significant difference between the groups. Although the severity of CH is a determinant for mental prognosis, the favorable effects of early onset of treatment on motor and cognitive functions cannot be ignored. Therefore, treatment at appropriate doses should be initiated as soon as CH is diagnosed without losing time for etiologic investigations.

Significant differences in serum TSH and FT4 levels have been reported between CH patients with thyroid dysgenesis and with dyshormonogenesis[7]. Since, among the patients in the PCH group, those with dysgenesis and suspected dyshormonogenesis also differed significantly in TSH levels at the time of diagnosis in our study, primarily PCH and thyroid dysgenesis as the etiology should be considered in patients, particularly in those with very high TSH levels.

In conclusion:

1-Both the rates reported in the literature and determined in our study seem to be higher than the estimated figures. The clinical relevance of this is that patients diagnosed with hypothyroidism are forced to receive avoidable long-term L-thyroxine treatment.

2-The presence of symptoms in patients at the time of diagnosis may suggest that the onset of the event had been during the intrauterine period, the exposure had an early onset, and the prognosis could be permanent.

3-Initial measurements of serum TSH and T4 may be a predictive factor in differentiating

PCH from TCH.

4-It should be borne in mind that the lower the dose of L-thyroxine required and the shorter the time needed for normalization of TSH levels, the higher the probability that the course of hypothyroidism will be transient in that particular patient.

5-Although the severity of CH is a determinant for mental prognosis, the favorable effects of early onset of treatment at appropriate doses on motor and cognitive functions should be borne in mind.

6-Studies with larger sample sizes are required to reveal any other unidentified factors that may affect the incidence of different forms of hypothyroidism.

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