RESEARCH PAPER

Neurodevelopmental Outcome of Children with Congenital Hypothyroidism Diagnosed in a National Screening Program in Turkey

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Objective: To study the factors affecting a neurodevelopmental status of children with congenital hypothyroidism, diagnosed on national screening program. **Methods:** The study was performed in the Pediatric Endocrinology Department of Dr. Behcet Uz Children's Hospital between May 2012 and May 2013. Children with congenital hypothyroidism, aged between 24 and 36 months, diagnosed by national screening program were included in the study group. Healthy subjects at the same age group consisted of the control group. For the neurodevelopmental evaluation, Bayley Scale of Infant Development- II (BSID-II) was used. Factors possibly effective on neurodevelopment were evaluated. **Results:** 42 patients and 40 healthy children (mean (SD) age, 29.4 (3.7) and 29.2 (3.5), respectively were included in the study. The mean MDI score [92.6 (7.07) *vs* 97.1 (9.69), *P*=0.14)] and the mean PDI score [97.8 (15.68) *vs* 99.1 (10.57), *P*=0.66)] in the study group and control group were not significantly different. Among the patient, 4.6% and 4.7% children were moderately retarded as per the MDI scores and PPI scores, respectively. The sex, socioeconomic status, birth weight, screening levels of TSH, severity of the congenital hypothyroidism, initiation time and the dosage of thyroid hormone replacement, length of the normalization period of TSH, and adherence to treatment were not found to affect the MDI and PDI scores of the patients.**Conclusion:** Some children with congenital hypothyrodism may have mild to moderate neurodevelopmental retardation, despite the early diagnosis and treatment, and thus need to be under regular follow-up for neurodevelopmental status.

Keywords: *Prognosis, Newborn screening, Neurodevelopment status.*

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A nationwide screening program for congenital hypothyroidism (CH) has been conducted in Turkey since December 2006. Early diagnosis and initiation of L-thyroxine replacement within two weeks of birth prevent irreversible neurological disability. However, patients have been reported with impaired neurodevelopment despite early diagnosis and treatment [4]. This condition is majorly considered to be owing to abnormal placental transport of thyroid hormones and intrauterine effects of hypothyroidism [5]. Factors such as socioeconomic status, birthweight, severity of the congenital hypothyroidism, the dosage of thyroid hormone replacement, length of the normalization period of TSH, adherence to treatment may also be contributive factors on neurodevelopmental impairment.

In this study we aimed to perform a neurodevelopmental evaluation of children with CH, diagnosed by the national screening programme endocrinology, between the ages of 2 and 3 years using Bayley Scale of Infant Development – II (BSID-II).

Methods

The study was conducted aftter approval of the Local Research Ethics Committee of Dr. Behcet Uz Children's Hospital, and written informed consent was taken from the parents of all study subject.

The study was conducted in the Pediatric Endocrinology Department of Dr. Behcet Uz Children's Research and Teaching Hospital between May 2012 and May 2013. Children with congenital hypothyroidism, aged 24-36 months old, diagnosed on national screening program were included in the study as the patient group. Patients born preterm were excluded. The control group consisted of healthy children admitted to pediatric polyclinics in the same age-group, who do not have the history of any perinatal or postnatal disease affecting central nervous system. Demographic profile of the children, gestational age, birth weight, history of maternal hypothyroidism, antithyroid drug usage on

pregnancy, the etiology of congenital hypothyroidism, level of TSH at the screening test, the severity of congenital hypothyroidism, age at the diagnosis, the initiation time of hormon replacement, the initial dosage of L-thyroxin, the length of the normalization period of TSH, the adherence to the treatment, socioeconomic status of the patients were recorded.

For TSH values, normal limits were taken as <10μmol/L in newborns, 0.5-5 μmol/L in other children. For free T4 (FT4) values, normal limits were taken as 1.17-2.64 ng/dL in newborns, 0,76-2 ng/dL in children between 1 month and 1 year old, 0.75-1.55 ng/dL in childen older than 1 year old. The severity of the disease was determined according to the initial FT4 levels (initial FT4 > 0.8 ng/dL mild disease, FT4 between 0.8 and 0.4 ng/dL moderate disease, FT4 ≤0.4 ng/dL severe disease). Socioeconomic status of parents were determined by the socioeconomical index developed by Nesanir and Eser [7]. For the neurodevelopmental evaluation BSID-II was used. Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) scores were calculated. In BSID-II, MDI and PDI have mean scores of 100 with a standard deviation of 15. Scores ≥85 were accepted as normal and below 85 were accepted as abnormal. Abnormal scores were categorized as given below: between 84 and 71 mildly delayed performance, between 70 and 50 moderately delayed performance, and below 50 severely delayed performance.

We used SPSS for Windows 19.0 for all calculations. The tests used were Pearson Chi-square test, Mann-Whitney U test, Student's independent t-test and Kruskal-Wallis test. Probability value of $P<0.05$ were considered to be significant. Factors possibly affecting neurodevelopmental outcome were evaluated by univariate analysis.

RESULTS

Forty three patients (23 males) with congenital hypothyroidism and 40 healthy subjects were included in the study. There were no significant diferrences in the baseline characterstics of the two groups (***Table* I**). Mothers of five patients had hypothyroidism and four of them had history of L-thyroxin replacement during pregnancy. Laboratory values and data about treatment of the patient group are given in ***Table* II**. Twenty nine of the patients (67.4%) had mild, 7 of the pateints (16.3%) had moderate and 7 of the patients (16.3%) had severe congenital hypothyroidism. The mean MDI score of the patient group 92.6 (17.1) was lower than the control group 97.1 (9.7), but this difference was not statistically significant ($P=0.14$). The mean PDI scores were similar in the two groups 97.8 (15.6) *vs* 99.1 (10.6) ($P=0.66$). As per MDI scores, 4.7% and 20.9% of the patients were found to be moderately and mildly retarded, respectively. In terms of the PDI scores, 4.7% each had moderate and mild retardation. There was no patient with severe retardation according to the both MDI and PDI scores.

Using univariate risk factor analysis; the sex, birth weight, level of TSH at the screening test,

TABLE I DEMOGRAPHIC PROFILE OF THE STUDY POPULATION

Parameter		*Patient group (n=43)*	*Control group (n=40)*
Age (mo)	Mean (SD)	29.4 (3.73)	29.3 (3.55)
Female, *n* (%)		20 (46.5)	18 (45)
Birthweight	Mean (SD)	3284.77 (479.33)	3152.50 (325.56)
Socioeconomic status, *n* (%)			
	High	2 (4.7)	2 (5)
	Medium	37 (86)	35 (87.5)
	Low	4 (9,3)	3 (7.5)

No statistically significant differences between the groups.

TABLE II DETAILS OF DIAGNOSIS AND TREATMENT AMONG CONGENITAL HYPOTHROIDISM PATIENTS

	Range	*Mean (SD)*
Screening level of TSH (μU/mL)	11.2-105	30.1 (23.15)
Age at diagnosis (d)	5-65	17.77 (12.51)
TSH level at diagnosis (μU/mL)	9.17-100.0	56.14 (32.56)
FT4 level at diagnosis (ng/dL)	0.08-2.19	0.97 (0.49)
At treatment initiation: Age (d)	6-66	20.4 (13.36)
L-Thyroxine dose (mcg/kg/d)	4-15	9.23 (3.59)

TABLE III RESULTS OF UNIVARIATE RISK FACTOR ANALYSIS

Parameter	*MDI score*	*PDI score*
Sex	0.08	0.09
Birthweight	0.90	0.61
Socioeconomic status	0.10	0.26
Level of TSH at the screening test	0.19	0.08
Severity of congenital hypothyroidism	0.54	0.13
Initiation time of hormone replacement	0.92	0.46
Initial dosage of L-thyroxine	0.57	0.54
Length of normalization period of TSH	0.54	0.79
Adherence to the treatment	0.96	0.20

MDI: mean developmental index; PDI: psychonotoe developmental index.

WHAT THIS STUDY ADDS ?

- In congenital hypothyroidism diagnosed by screening programme, some patients may have mild to moderate neurodevelopmental retardation, despite early diagnosis and treatment.

socioeconomical status, the severity of congenital hypothyroidism, the initiation time of hormone replacement, the initial dosage of L-thyroxin, the length of the normalization peirod of TSH, and the adherence to the treatment were not found to be significantly associated with different MDI and PDI scores (***Table* III**).

DISCUSSION

In this study of 43 infants diagnosed at birth with congenital hypothyroidism, 16.2% with CH were symptomatic, and the most common symptom was prolonged jaundice. Their neurodevelopmental status follow-up was not significantly different from normally developing peers.

The New England Congenital Hypothyroidism Collaborative reported no apparent specific impediments to learning in such children at 9-10 years of age [8]. In a meta-analysis [9], patients with CH detected by neonatal screening and treated from early age had been evaluated for neuropsychologic development. It showed a trend toward lower intelligence quotient (IQ) and poorer motor skills in CH patients compared with controls [9]. Pooling of the data demonstrated a significant deficit of the mean IQ of 6.3 (95% confidence interval 4.7-7.8) [9]. The most important factor for IQ deficit was found as the severity of the CH. Similar to these findings, some mildly and moderately retarded patients were detected in our study, despite the early diagnosis and treatment. These results suggest that at least part of brain damage in patients with CH is caused *in utero* and can not be prevented by early treatment.

The severity of CH has been reported to be associated with neurodevelopmental impairment in patients diagnosed by neonatal screening program [10,11]. Our study did not find a significant association with the severity of CH and neurodevelopment, but children in mild CH group had higher mean MDI scores than the moderate and severe CH group and had higher mean PDI scores than severe CH group. In the literature, early initiation of hormone replacement has been shown to positively affect the neurodevelopment [12]. In a review identfying 11 studies evaluating the age of onset of thyroid hormone treatment, infants started "early" (12 to 30 days of age) had been found to have higher IQ scores than infants started "later" (>30 days of age) [14]. In our study, mean (SD) treatment initiation time was not in the "later" category, 20.4 (13.4) days, and MDI and PDI scores did not change with the initiation time of hormone replacement. The effect of the initial dosage of L-thyroxin and the length of the normalization period of TSH on motor and mental development are controversial in the current literature [4,13], and we did not find any effect of the dose. The adherence to treatment is an important factor for neurodevelopmental prognosis [14]; however, we could not find significant association between the adherence to treatment and MDI or PDI scores. Socioeconomical status is also an important factor on neuromotor development [15]. In our study 91% of the patients had medium and high socioeconomical status so MDI and PDI scores were not significantly different.

Babies diagnosed with CH in a national screening program should be under regular follow up for neurodevelopmental status by a multidisciplinary team.

Contributors: BE, BTB, KD, EO, BO: involved in the management of patients; BT: planned the study, collected data, performed statistical analysis and drafted the manuscript; BE: involved in planning of the study and reviewed the script; BB: involved in statistical analysis; FG: involved in planning the study, critically reviewed the manuscript and would act as the guarantor of the study.
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