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Original article

Neurodevelopment evaluation in children with congenital hypothyroidism by Bayley-III ☆

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Abstract

Background: Congenital hypothyroidism is the most common reason of mental retardation, and normal neurological development can be provided by early and effective treatment. In this present study, it is aimed to compare neurological developments of patients in 6–42 months of age with congenital hypothyroidism and healthy controls of the same age group prospectively by Bayley III test. *Methods:* In this present study, neurological developments of 41 congenital hypothyroidism cases and 39 healthy controls, who applied to Pediatric Endocrinology Section of Mersin Children Hospital and Pediatric Neurology Outpatient Clinic of the Medical School at Mersin University between years 2009 and 2011, were evaluated by Bayley III test. *Results:* Cognitive, language and global motor scores in addition to receptive communication, expressive communication, fine motor and gross motor subscores in children with congenital hypothyroidism were statistically significantly lower than those in the control group ($p < 0.05$). It is detected that initiation dose and day of treatments, severity of hypothyroidism and time to normalization thyroid stimulating hormone had no statistically significant effects on neurological development of the study group ($p > 0.05$). In both groups, as the education levels of mothers are increased, language development scores are also increased ($p < 0.05$). Additionally, statistically significant increases in Bayley III scores except cognitive scores have been observed in both groups as the level of income is increased ($p < 0.05$). *Conclusions:* Despite early and effective treatment in newborns with congenital hypothyroidism, retardation in neurological developmental has been detected. This situation can be related to influences on neurodevelopment in intrauterine period. According to our present knowledge, this study is the first case–control study in the literature that neurological developments of congenital hypothyroidism patients are evaluated with Bayley-III score.
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Keywords: Congenital hypothyroidism; Bayley-III score; Neurological development

1. Introduction

Congenital hypothyroidism (CH) is the most common preventable cause of mental retardation. It is the most commonly encountered endocrinopathy in the world with a rate of 1/2000–1/4000 [1]. Before the routine screening program, since signs are reflected lately to the clinics, severe mental retardation cases due to late diagnosis and treatment have been observed in patients. However, in recent years as CH screening has been widespread in newborns, treatment can be started in the first 1–2 weeks of life. As a result of this, although severe mental retardation is not a common sign, mild intellectual deterioration, neurocognitive and behavioral disorders

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can arise [2–4]. It has been reported that there is an important correlation between effects of neurological development, and initiation age of treatment, initiation dose of treatment, severity of hypothyroidism, time to normalization thyroid stimulating hormone (TSH) and socioeconomic level [2–6].

"Bayley Scales of Infant and Toddler Development Screening Test, Third Edition" (Bayley III) is one of the most reliable and widely used tests for growth retardation in children aging 1–42 months. This test is first described in 1969 by Bayley. It is revised in 1993, and lastly it is standardized in 2006 again by Bayley [7–9]. Cognitive, language and global motor development of infants and children are being evaluated by Bayley-III test. Language scale is evaluated by two subscores; expressive and receptive communications, as well as the motor development, which is evaluated also by two subscales; fine and gross motor scores [9].

In this present study, it is aimed to compare neurological development of CH patients, who are diagnosed during newborn period through the national thyroid screening program by pediatric endocrinologists, and were aging from 6 months to 42 months, with healthy controls by using Bayley-III test. Additionally, it is also planned to investigate significance of Bayley-III test, effects of early diagnosis and effective treatment of CH on the neurological development.

2. Materials and methods

In this present study, 41 CH cases, which are followed up at Pediatric Endocrinology Section of Mersin Child Hospital and Pediatric Neurology outpatient clinics of Mersin University Medical School between years 2009 and 2011, are prospectively investigated. All patients had high TSH (>15 mIU/L) level by neonatal screening and transferred to pediatric endocrinology department. Control group is randomized from children in 6–42 months age group, who had normal TSH in the hypothyroidism screening program without any health problems, and is followed up in the General Pediatrics outpatient clinic. Children with preterm birth history, genetic syndrome, any neurological diseases (mental-motor retardation etc.), and children younger than 6 months and older than 42 months were all excluded from the study. Ethics committee approval was provided from Medical School of Mersin University before initiation of the study.

All demographic characteristics (age, gender, and birth weight, weight during the test, length, head circumference (HC), parental age, and income level) of patient and control groups have been recorded. CH is diagnosed as decreased free T4 (fT4) with high TSH (>20 mIU/L) [1,10]. Na L-thyroxin (L-T4) was started 7.5–17 μg/kg/day (once daily, before meal in the morning) in patient with CH according to severity of disease and serum fT4/TSH levels at the time of diagnosis. Patients classified into two groups based on L-T4 starting time (before and after 15 days). Patients are asked for his first control 15 days after the diagnosis, and they are followed up once a month until 6 months of age; every 2 months in 6–12 months period; and every 3 months in 12–42 months at our pediatric endocrinology outpatient clinic with the parameters of weight, length, head circumference, fT4, and TSH. Moreover, the date of CH diagnosis; first TSH and fT4 values; initial treatment dose; TSH and fT4 values at months 3, 6, 9, 12 and Bayley-III test; and bone age are all recorded.

Weight is measured using balance with 10-g precision (Seca Model 345) and recumbent length is measured to 0.01 cm using a digital infantometer (447 Infantronic Digital Infantometer, Quickmedical) in under 2 years old children. However, in the group older than 2 years, length is measured to the nearest centimeter using a rigid stadiometer (Holtain limited, United Kingdom) and weight is measured unclothed to the nearest 0.1 kg using a calibrated balance scale (Seca, Germany). Head circumference is measured with a non-elastic tape line at the largest diameter. Standardized measures for Turkish children have been used for weight, length, body mass index (kg/m^2), and head circumference, and Standard deviation scores (SDS) are calculated for each measurement [11]. Laboratory analysis of, fT4 and TSH levels are performed with commercial test kits (Roche Cobas®) using Elecsys 2010® analyzer. The corresponding normal values for the 2.5 and 97.5 percentiles of, fT4 and TSH were 0.82–1.7 ng/dL, and 0.27–4.2 μIU/mL, respectively. Thyroid ultrasonography (US) was obtained for all infants with CH before thyroxin replacement therapy. Tc-99m thyroid scintigraphy (TS) was performed in patient with abnormal thyroid US. On the basis of thyroid US and Tc-99m TS, CH was classified as dysgenesis (ectopy, agenesis or hypoplasia) and dyshormonogenesis (normal thyroid gland). Patients who had dysgenetic gland and/or serum fT4 level lower than detectable level (0.3 ng/dL) assessed to have severe CH.

Cognitive, language and global motor developments are evaluated in infants and children by Bayley-III test. While language scale has been evaluated by two subscores, expressive and receptive communications, motor development is evaluated also by two subscores; fine and gross motor scores. The cognitive scale includes information processing, information processing speed, problem solving, play skills and number concepts. The language scale includes both receptive (ability to hear, understand, and respond) and expressive (ability to communicate) communication skills. The motor subtests include quality of movement, sensory and perceptual motor integration, and basic locomotion milestones. The Bayley-III composite test scores are scaled on a range of 40–160, to have a mean of 100, and an SD of

15. Although not considered an intelligence quotient test, the Bayley Scales reliably identify infants with developmental delays, as indicated by scores less than 85 on the cognitive, language, or global motor composite scores [9]. Tests were performed by one individual (K.M.), who is experienced in testing the child development, and is blinded to the thyroid status of participant. Each test has been completed approximately in 60–120 min. Test forms are completed in details and are evaluated by scoring.

2.1. Statistical analysis

After data are entered into SPSS 11.5 package program, normality controls of continuous measurements were performed by Shapiro–Wilk test. Differences between continuous measurement groups were tested by Student's *t* test, Mann–Whitney *U* and Kruskall–Wallis tests. Mean and Standard deviation values were given as descriptive statistics. Duncan's test was used for post hoc test. Bivariate relationships between categorical variables were examined using Pearson's Chi-squared test or Likelihood ratio tests. Numbers and percentages were given as descriptive statistics. Correlation between continuous measurement values was tested by Spearman correlation coefficient. The results were considered statistical significance if p values were less than 0.05.

3. Results

A total of 80 cases, 41 patients and 39 controls, were enrolled into the study. The mean age of the patients at the time of CH diagnosis was 14.3 ± 8.2 days old. In study time, mean age of patients and controls was 18.7 ± 9.5 and 18.0 ± 8.7 months ($p = 0.726$) respectively. At time of study, SDS values of weight, length and HC of patients were -0.3 ± 1.04, -0.2 ± 0.9, and 0.2 ± 1.1 respectively and weight, length and HC SDS were -0.2 ± 0.65, 0.1 ± 1.1, and 0.1 ± 0.9 respectively in controls. There were no difference between patients and controls for all antropometric data at the time of study ($p > 0.05$). Five (12.1%) of the patients had jaundice, and two (4.8%) had drowsiness. No patient had clinical symptoms or findings (hypotonic posture, myxedematous facies, macroglossia etc.) for severe CH. In this study, we detected four (9.7%) dysgenetic thyroid gland (two ectopy and two agenesis) in patient with CH. At the time of CH diagnosis, the mean TSH and fT4 levels were 95.72 ± 54.32 mIU/L and 0.55 ± 0.42 ng/dl, respectively.

There was no statistically significant difference in age, gender, birth weight and parental ages, parental education levels and income levels between patient and control groups (Table 1).

While Bayley-III test is applied on the entire control group, four cases in the patient group are excluded because they were not compliant with the test. Mean values of cognitive, language and global motor scores in addition to their subscores, namely receptive communication, expressive communication, fine motor, gross motor scores, was shown in Table 2. Statistically significant retardation has been detected in all scores in patient group rather than the controls (Table 2).

There was no statistically significant difference in Bayley-III scores of participants, whose treatment initiation date was before and after 15 days. Descriptive statistical values (mean and standard deviation) and p values are given in Table 3.

There was no statistically significant difference in Bayley-III scores in patients, who had initial doses of L-T4 treatment as 7.5–12.0 μg/kg/day and 12.1–17.0 μg/kg/day. Descriptive statistics and p values are given in Table 3.

When Bayley-III scores are investigated in participants with normal (dyshormonogenesis) and abnormal (dysgenesis) thyroid ultrasonography examinations, and similar results in scores have been observed (Table 3).

When differences between maternal education level and Bayley-III scores are investigated, there was statistically significant differences in the educational status in language (general), receptive communication and expressive communication (Table 3). As educational level is increased, mean values of these scores are also observed to increase.

Table 1
Demographic data of patients and the control group.

	Patient	Control	*P*
Gender			
Female	16 (39.0)	19 (48.7)	0.382[a]
Male	25 (61.0)	20 (51.3)	
Education level of mother			
Primary school	8 (19.5)	6 (15.4)	0.612[b]
High school	31 (75.6)	29 (74.4)	
University	2 (4.9)	4 (10.3)	
Education level of father			
Primary school	7 (17.1)	3 (7.7)	0.215[b]
High school	22 (53.7)	28 (71.8)	
University	12 (29.3)	8 (20.5)	
Age (months)	18.7 ± 9.5	18.0 ± 8.7	0.726[c]
Birth weight (g)	3325.61 ± 392.98	3365.13 ± 353.52	0.638[c]
Mother's age (years)	30.2 ± 6.2	30.1 ± 6.2	0.958[c]
Father's age (years)	35.4 ± 7.1	34.4 ± 5.6	0.474[c]
Income level (TL*)	964.02 ± 531.33	1033.33 ± 536.60	0.149[d]

1 TL* = 0.56$.
[a] p Value related to Pearson Chi square test.
[b] p Values related to Likelihood ratio Chi square test.
[c] p Values related to Student's t-test.
[d] p Value related to Mann–Whitney U test.

Table 2
Comparison of neurological development scores of patients and the control group.

	Patient ($n = 37$)	Control ($n = 39$)	P
Cognitive	93.24 ± 8.76	102.95 ± 10.68	<0.001[d]
Language	95.35 ± 6.48	109.31 ± 12.52	<0.001[c]
Receptive communication	10.19 ± 1.33	12.87 ± 2.44	<0.001[c]
Expressive communication	8.24 ± 1.34	10.31 ± 2.26	<0.001[c]
Global motor	97.73 ± 10.00	103.82 ± 19.73	0.008[d]
Gross motor	10.73 ± 2.08	12.18 ± 2.60	0.009[c]
Fine motor	8.46 ± 2.45	9.85 ± 2.43	0.014[d]

[c] p Values related to Student's t-test.
[d] p Values related to Mann–Whitney U test.

Moreover, there was no statistically significant correlation between initial day of treatment, first TSH and fT4 levels, and all scores in the patient group ($p > 0.05$). Also no statistically significant correlation is detected between TSH and fT4 levels at the time of diagnosis, months 3, 6, 9, 12 and during Bayley-III test, and all scores ($p > 0.05$). There was no statistically significant correlation between time to normalization TSH and Bayley-III scores ($p > 0.05$). However, correlation between the income levels and Bayley-III scores are investigated, and no statistically significant increase has been observed in Bayley-III scores excluding the cognitive score (Table 4).

4. Discussion

CH screening program in newborns has become a standard procedure in many countries in the world. In Turkey, the Ministry of Health has started CH screening in newborns since 2006. Frequency of severe complications due to CH is decreased very much by early diagnosis and treatment as the result of CH screening in newborns. Although severe mental retardation is not observed frequently, mild intellectual disorders, neurocognitive and behavioral disorders can be encountered. Neurological developments of CH patients have been investigated in many studies [2–6]. According to our present knowledge, this study is the first case–control study in the literature that neurological developments of CH patients are evaluated with Bayley-III score.

Neurological development in children is influenced by many factors including environmental factors [12]. In the current study, there was no statistically significant difference in age, gender, birth weight, parental ages, parental education levels and socioeconomic status between the case and control groups. As a result, both groups were similar in environmental factors influencing neurological development.

In the first trimester maternal thyroid hormons are effective on development of fetal brain, while continuing development of the brain in the second and third trimesters relies increasingly on thyroid hormones produced by both the fetus and mother [13]. Although effects of thyroid hormones on the brain development starts from

Table 3
Initiation day of treatment, initiation dose of drug and severity of hypothyroidism, Bayley III scores and statistical data of the patient group. Mother's education levels in patient and control groups, Bayley III scores and statistical data.

		Cognitive	Language	Receptive communication	Expressive communication	Global motor	Gross motor	Fine motor
Treatment initiation day	<15 days	94.2 ± 10.7	95.9 ± 6.7	10.6 ± 1.4	8.1 ± 1.4	97.4 ± 8.7	11.0 ± 1.9	8.1 ± 2.2
	>15 days	92.2 ± 6.2	94.8 ± 6.3	9.8 ± 1.2	8.4 ± 1.3	98.1 ± 11.5	10.4 ± 2.3	8.8 ± 2.7
	P[a]	0.498	0.607	0.066	0.382	0.850	0.424	0.373
Initiation dose of drug (μg/kg)	7.5–12.5	92.0 ± 8.6	94.9 ± 6.8	10.1 ± 1.4	8.2 ± 1.6	99.0 ± 9.5	10.5 ± 1.8	9.2 ± 2.9
	12.5–17.5	95.0 ± 9.4	95.5 ± 6.4	10.2 ± 1.3	8.3 ± 1.1	97.7 ± 10.5	11.4 ± 2.4	7.8 ± 1.6
	P[a]	0.336	0.781	0.829	0.688	0.715	0.181	0.110
Severity of hypothroidism	Dys-hormonogenesis (n: 31)	92.6 ± 8.3	95.0 ± 6.6	10.1 ± 1.4	8.2 ± 1.4	99.1 ± 9.3	10.9 ± 2.0	8.7 ± 2.5
	Dysgenesis (n: 4)	98.8 ± 13.8	96.5 ± 6.2	10.5 ± 1.3	8.3 ± 1.0	93.3 ± 13.7	10.3 ± 2.9	7.5 ± 1.9
	P[a]	0.201	0.672	0.576	0.974	0.265	0.539	0.363
Education level of mother	Primary school	98.3 ± 9.6	100.3 ± 15.9	10.9 ± 2.8	9.2 ± 2.7	96.7 ± 12.2	10.5 ± 2.6	8.4 ± 2.4
	High school	97.0 ± 10.1	101.6 ± 10.7	11.5 ± 2.3	9.07 ± 1.85	100.3 ± 15.7	11.5 ± 2.2	9.1 ± 2.2
	University	110 ± 15.2	116 ± 11[*,†]	13.5 ± 1.8[*]	11.8 ± 2.0[*,†]	114.8 ± 20.2	13.2 ± 4.0	11.7 ± 4.3
	P[e]	0.102	**0.017**	**0.037**	**0.020**	0.077	0.155	0.431

$p < 0.05$: statistically significant
[a] p Values related to Student's t-test.
[e] p Values related to Kruskall–Wallis test.
[*] Differences with the primary school.
[†] Differences with the high school.

Table 4
Relationships between the income level and Bayley-III scores.

		Cognitive	Language-general	Receptive communication	Expressive communication	Global motor	Gross motor	Fine motor
Income level	*r*	0.194	0.326	0.316	0.267	0.358	0.249	0.252
	p	0.092	**0.004**	**0.005**	**0.020**	**0.002**	**0.030**	**0.028**

$p < 0.05$: statistically significant

the intrauterine life and continues until 2–3 years of age, first 6 months in the postnatal period is known to be a very important time interval [13]. Klein et al. have first reported the negative effect of CH in IQ points, which were 89 (64–107) if treatment is initiated at birth to 3 months of age; 71 (35–96) if it is initiated in 3–6 months of age; and 54 (4–80) if it is initiated after 6 months of age, and five points of decrease for every month [14]. Effects of treatment initiation age on mental-motor development are still debatable. LaFranchi et al. have reported in their meta-analysis study of 11 trials that higher IQ points are detected in patients, who received the treatment before 30 day old than the ones started after 30 days [15]. However, Connelly et al. have reported that similar IQ points have been detected in patients, who received the treatment before and after 14 days [16]. Dimitropoulos et al. reported that there was no correlation between treatment initiation age and IQ points [17]. Kempers et al. reported that severity of CH was more determining on long term cognitive and motor functions rather than the treatment initiation time [18,19]. In our study, patients are divided into two; treatment initiation time before and after 15 days of life. There was no statistically significant difference between two groups in cognitive, language, global motor, expressive communication, and receptive communication, fine motor and gross motor scores determined by Bayley-III test (Table 3). Although CH is treated at an earlier phase neurodevelopment deficits may appear. This situation can be related to influences on neurodevelopment in intrauterine period.

Treatment initiation dose effects of CH on mental and motor developments are still debatable. In a meta-analysis of 10 studies, six studies indicated that higher the treatment initiation dose higher IQ levels; two studies indicated that treatment initiation dose had no effects; and the remaining two studies revealed that lower the dose of treatment, higher the IQ level [15]. Dimitropoulos et al. reported that treatment initiation dose had no effect on IQ level [17]. Huo et al. reported that doses of 10–12.5 and 12.6–15 μg/kg/day had no statistically significant effect on development scores [20]. There was no statistically significant difference between treatment initiation doses of <12 μg/kg/day (7.5–12.0); >12 μg/kg/day (12.1–17.0) and Bayley-III scores (global motor, language, cognitive, fine motor, gross motor, receptive communication, expressive communication) (Table 3).

Severity of CH disease changes depending on the underlying etiology. There have been many studies investigating the relationship between hypothyroidism severity and mental motor development [5,19,20,22,23]. Derksen-Lubsen et al. compared 670 children with CH and 570 controls in their meta-analysis, which included seven studies, and reported that IQ point of children with CH is lower at a mean of 6.3 points than that of the controls [21]. In the observation study of Oerbeck, it is reported that IQ score in children with severe hypothyroidism (T4 < 2) was 16 points lower than that in children with moderate hypothyroidism [5]. Bargagna et al. detected neurological scores in children with severe CH were significantly lower than that of in children with mild CH and the controls [22]. In Tillotson's trial, IQ level is reported 11.6 points lower in patients with T4 < 3.3 rather than the ones with T4 > 3.3 [23]. In our study, severity of CH did not statistically significantly affect Bayley-III scores. This situation is believed to be related to the fewer number of patients compliant with the severe CH definition (four patients).

Time to normalization of TSH in CH is reported to be a relevant factor on neurological development [15,24,25]. There are studies indicating that longer time to normalization of TSH than 3 months causes severe neurological development defects [24,25]. In our study, time to normalization of TSH did not have statistically significant effects on Bayley-III scores. This situation is believed to be due to normalization of TSH in all patients at the first control visit (in the 1st month) after treatment initiation.

Socioeconomic level is an independent factor affecting mental-motor development. Socioeconomic factors like parental age, education level and income level of family have been demonstrated to have prominent effects on neuromotor development of children in many studies [12,26]. In our study, CH and control groups were similar in parental age, education level and income level. In both groups, significant correlation was detected between maternal education level and language, receptive communication and expressive communication; as the education level of mother is increased,

points are also increased (Table 3). As parental age is increased, Bayley-III scores are decreased, but this was not statistically significant. Moreover, as the income level is increased, Bayley-III scores other than cognitive score are statistically significantly increased in both groups (Table 4). Dimitropoulos et al. reported that low socioeconomic level was a deteriorating factor in neuromotor development of children especially with CH [17]. However, in our study, low socioeconomic level showed a deteriorating factor in neurodevelopment in CH patients and also control group.

In conclusion, despite early diagnosis and treatment, neuromotor development retardation has been detected in newborns with CH. This situation can be related to influences on neurodevelopment in intrauterine period. Socioeconomic level is demonstrated to have prominent effects on neurological development of children with CH, like in the entire population. We think that this study will contribute into the literature as it is the first case control study performed with Bayley-III on children with CH.

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