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Risk factors for neurodevelopmental deficits in congenital hypothyroidism after early substitution treatment

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Abstract. Neurodevelopment in children with congenital hypothyroidism who receive early treatment is generally good. However, subtle neurological deficits still exist in some patients. The aim of this investigation was to evaluate factors that may influence neurodevelopmental outcome in congenital hypothyroidism patients. The developmental quotient (DQ) of 155 children with congenital hypothyroidism was evaluated at 24 months of age, using Gesell Developmental Schedules (GDS), and compared with that of 310 healthy controls. Mean DQ scores in congenital hypothyroidism patients were 7.5 points lower for adaptive behavior than in control patients ($p < 0.01$). Patients with severe congenital hypothyroidism had the lowest DQ scores compared with two other congenital hypothyroidism subgroups and controls ($p < 0.01$). Children with congenital hypothyroidism who also had a low level of serum T_4 at diagnosis or exhibited a longer thyroid stimulating hormone (TSH) normalization time had lower adaptive behavior scores ($p < 0.0003$). Bivariate correlation and multiple regression analyses found that the severity of congenital hypothyroidism and parental socioeconomic status correlated with DQ scores. TSH normalization time was negatively related to adaptive behavior scores ($p < 0.01$). Neurodevelopmental deficits in children with congenital hypothyroidism correlate with the severity of congenital hypothyroidism, TSH normalization time, and parental socioeconomic status.

Key words: Congenital hypothyroidism, Neonatal screening, Developmental quotient

CONGENITAL hypothyroidism (CH) is the most common preventable cause of mental retardation [1]. CH screening in newborns and early levothyroxine (L-T_4) substitution treatment from early life has dramatically improved the outcomes of intellectual potential and linear growth in children with CH [2-4]. However, even in patients with CH who receive early treatment, subtle selective cognitive deficits and some signs of minimal brain damage (including impairment of mathematical ability, cognitive performance, speech, learning, and fine motor coordination in later life) have been reported in some studies [5-9]. It has been reported that the specific deficits depend on the etiology of hypothyroidism, as well as the starting time and the dosage of replacement hormone therapy [3, 10, 11]. Therefore, efforts should be on going made to establish the optimal therapy that leads to the possibility that children with CH reach their complete intellectual potential. Experimental studies at the cellular level found that hypothyroidism impaired neuronal progenitor proliferation and migration, which may contribute to persistent cognitive deficits and learning impairments [12-14]. Furthermore, cell proliferation, neuronal differentiation, and cognitive function are environmentally related and could be stimulated and improved by environmental stimulation [15]. The aim of the present study was to evaluate developmental quotient (DQ) of CH infants treated within the first month of life and analyze risk factors associated with neurodevelopmental deficits in order to predict intellectual development.

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Subjects and Methods

Newborn screening program

A drop of plantar blood was taken from newborns from 3 to 5 days after birth, put onto a filter paper, and mailed to Henan Neonatal Screening Center for measurement of thyroid stimulating hormone (TSH) by the Auto-DELFIA method. Repeated measurement from the same filter paper sample was performed in duplicate if TSH was greater than 15.0 mIU/L. A repeat TSH measurement greater than 15.0 mIU/L was considered indicative of CH and was immediately referred for biochemical and clinical evaluation. Diagnostic confirmation is performed through measurements of serum TSH, T_4, and FT_4 by chemiluminescence (normal values for infants at 2-4 weeks of age are < 10 mIU/L, approximately 90-206 nmol/L, and 10-26 pmol/L, respectively) [16]. Diagnosis of CH was made as serum TSH >10 mIU/L with or without low serum thyroxine. The severity of CH was classified into subgroups according to initial serum T_4 level (severe: initial serum T_4 < 30 nmol/L; moderate: initial serum T_4 30-60 nmol/L; and mild: initial serum $T_4 \geq 60$ nmol/L). Replacement therapy with L-T_4 was started once diagnosis was made. TSH was retested every month and every three months, and serum thyroid function test every three months and every six months when the patients were before and after 2-year-old, respectively. The dosage of L-T_4 was adjusted according to the results of tests by the pediatric endocrinologists at the pediatric clinic of the Third Affiliated Hospital of Zhengzhou University.

Subjects

Of the 613912 newborns screened during the period between 2001 and 2008, 198 infants were detected with CH in Henan province, China. Of these 198 infants with CH, 155 infants were admitted to our study according to the following inclusion criteria: newly diagnosed cases of CH confirmed by a pediatric endocrinologist; gestational or adjusted gestational age $\geq$ 37 weeks; onset of therapy by the first month of life; initial L-T_4 dosage ranging from 10 to 15 μg/kg/day; availability of both thyroid ultrasound and/or scanning or knee X-rays, which had already been performed at the time of initiation of treatment, in order to assess either etiology of CH or neonatal skeletal maturity; availability of a DQ assessment at an average age of 24 months (range: 18.1-29.9 months, median: 24.1 months) [17].

Control subjects were chosen based on the following inclusion criteria: came from the same geographic area, born at term and were prospectively followed from birth and at the same age intervals as the CH patients during the same period. CH patients and controls had no neonatal risk factors for adverse outcome or other disorders known to influence mental development such as birth asphyxia and congenital malformations. In addition, the developmental pediatricians who examined the children with CH performed the neurodevelopmental examinations of the controls around 24 months of age (range: 18-30 months of age). Altogether 310 children (151 girls and 159 boys) fulfilled the criteria were selected.

Characteristics of CH patients

The following data were collected for new CH cases using a standardized clinical questionnaire and clinical evaluation at diagnosis. These include anonymous data concerning CH infants, such as screening and confirmatory laboratory tests, information on demographic data, details regarding clinical state during the neonatal period, diagnostic investigations (biochemical determinations, bone age, thyroid ultrasound, and/ or scintigraphy); information regarding pregnancy, birth, and family background; age at screening; and starting day and dose of replacement therapy. All confirmed CH patients were examined by color doppler ultrasonography, and the 155 patients included in the study were classified as having athyreosis, dysgenesis (ectopy or hypoplasia), and orthotopic /dyshormonogenesis (normally sited and shaped gland).

Bone age was determined from X-rays of the knees of newborn infants (before or 1-3 days after the start of therapy) and was defined as normal if its diameter exceeded 3 mm or retarded when the bony nucleus of the distal femoral epiphysis was absent or its diameter was < 3 mm in children born full term or with corrected gestational age of more than 37 weeks [18]. Of the 155 included cases, knee X-rays were conducted in 124 cases.

Parental socioeconomic status (SES) was estimated based on parental occupation and maternal education [2, 19]. SES scores ranged from 2 (lowest SES) to 12 (highest SES). There is no difference in mean SES between the two cohorts (CH cohort 8.0 *versus* control cohort 8.3, $p > 0.05$).

Neurodevelopmental assessment

All subjects were examined with the Gesell

Table 1. Characteristics of the CH patients in the study at the beginning of treatment stratified for severity

		Total CH(*n*=155)	Severe CH (*n*=89)	Moderate CH (*n*=45)	Mild CH (*n*=21)
Gender (female/male)	Number	88/67	53/36	23/22	12/9
SES*	Median (range)	8(4-12)	8(4-10)	7(4-12)	7(4-12)
Birth weight (g)	Median (range)	3502(2204-4604)	3504 (2204-4604)	3449 (2483-4102)	3609 (2489-4483)
Gestational age (weeks)	Median (range)	40.2(37.9-42.8)	40.2(37.9-42.8)	40.1(38.4-42.5)	40.3(38.7-41.3)
Serum T_4 at diagnosis (nmol/L)	Mean (range)	31.0(0.01-110.4)	13.9(0.01-29.36)	42.3(30.0-58.9)	78.8 (60.0-110.4)
Retarded bone age at diagnosis	Number	66 (43%)	55** (62%)	11(24%)	0
Type of CH					
Athyreosis	Number	41(26%)	37** (42%)	4(9%)	0
Dysgenesis	Number	85(55%)	44(49%)	31(69%)	10(48%)
Orthotopic/dyshormonogenesis	Number	29(19%)	8(9%)	10(22%)	11(52%)
Therapy onset (days)	Median (range)	19 (12-27)	19 (12-27)	19 (13-27)	20 (14-26)
Initial L-T_4 dose (μg/kg /day)	Median (range)	12.4 (10-14.9)	12.5 (10-14.9)	12.3 (10.1-14.7)	12.5 (10,3-14.8)
Age at DQ assessment (months)	Median (range)	24.1(18.1-29.9)	23.9(18.1-29.6)	24.1(18.2-29.8)	24.1(18.2-29.9)

* Parental socioeconomic status; ** $p < 0.01$ *vs.* moderate and mild CH.

Developmental Schedules (GDS) at around 24 months (18-30 months). The GDS has been adopted by Chinese Pediatric Association and is widely used for evaluating early child development (4-36 months) [20, 21]. The GDS provide an estimate of overall development considering five specific intellectual and behavioral functions: adaptive behavior, gross motor, fine motor, language, and personal-social behavior aspects. Each child is assigned a DQ in each of the five areas. This evaluation was carried out by fixed pediatricians from the Children Development Center of the Third Affiliated Hospital of Zhengzhou University and the pediatricians were blind to the status of the children—normal *vs* hypothyroid. This study was approved by the Ethics Committee at the Third Affiliated Hospital of Zhengzhou University.

Statistical analyses

Descriptive statistics were calculated for the characteristics and DQ scores of the CH subjects. For statistical purposes, Student's unpaired *t*-test, Mann–Whitney's test, or the chi-square test were used when appropriate to estimate difference between groups. Correlations were performed to explore the relationship between the DQ scores and the characteristics in CH subjects by Pearson's test. Data from the 155 CH subjects were combined and multiple regression analyses were conducted to investigate the associations among DQ scores and the characteristics in CH subjects. For all analyses, the two-tailed *p* value for statistical significance was 0.05.

Results

Characteristics of CH patients at the beginning of treatment

The demographic, neonatal, and pretreatment endocrinological variables of the 155 CH children were divided into subgroups according to serum T_4 value for the confirmation of the screening results, and are shown in Table 1. There are no differences in gender, SES, birth weight, gestational age, day of therapy onset, initial L-T_4 dose or age at DQ assessment among the subgroups. However, the percentage of athyreosis (47%) is significantly higher in patients with severe CH than in those with moderate (4%) or mild CH ($p < 0.01$). Retarded skeletal maturity is more common in children with severe CH (62%) ($p < 0.01$).

Neurodevelopmental outcome at 24 months

The total mean DQ scores in the CH group were within the normal range, and there were no significant differences compared with the control group, even though the scores were low in the CH group (Table 2). The mean difference was 7.5 points for adaptive behavior. The severe CH subgroup had the lowest DQ scores compared with the other two subgroups and the control group ($p < 0.01$).

Based on DQ scores of adaptive behavior, 32% (n = 49/155) in the CH group compared with 17% (n = 53/310) in the control group ($p = 0.0003$) had DQ scores lower than 1 SD of the mean of the control group. Moreover, 8% (n = 12/155) of CH patients compared with 2% (n = 7/310) of control subjects had DQ scores lower than 2 SD of the mean ($p = 0.005$). The CH chil-

Table 2 DQ scores[a] of the CH patients in the study at 24 months of age[b]

	Adaptive behavior	Fine motor	Gross motor	Language	Personal-social behavior
Severe CH (*n*=89)	92.35±11.74[c,d]	88.88±12.97 [c,d]	90.38 ±15.27 [c,d]	88.73±14.50 [c,d]	90.36±14.19 [c,d]
Moderate CH (*n*=45)	97.87±9.72	97.02±12.53	98.76±17.49	96.36±14.79	96.36 ±14.79
Mild CH (*n*=21)	100.95±11.05	99.24±15.54	100.52±17.26	99.24±15.54	100.05 ±12.06
Total CH (*n*=155)	95.12±11.53	92.65±13.86	94.19±16.71	92.37±15.26	93.41 ±14.51
Controls (*n*=310)	102.64±13.34	101.38±15.21	103.73±12.30	100.35±15.34	103.11±14.32

[a] DQ scores are expressed as the mean ± SD; [b] There is no age difference among mild, moderate and severe CH groups.
[c] $p < 0.01$ *vs.* mild CH; [d] $p < 0.001$ *vs.* control group.

Table 3 Comparison of CH with DQ*<1 SD and DQ*≥1SD of the mean of control at 24 months of age

		DQ* < 1 SD	DQ* ≥ 1SD	*p*
Gender	Female percent	71%	50%	$p = 0.012$
SES**	Median (range)	7(4-12)	8(4-12)	n.s.
Birth weight(g)	Median (range)	3511 (2483-4510)	3491 (2204-4630)	n.s.
Gestational age	Median (95% CI)	40.2(37.9-42.8)	40.2(38.4-41.9)	n.s.
Serum T_4 at diagnosis(nmol/L)	Mean ±SD	21.09±21.24	35.52±24.78	$p = 0.0003$
Retarded skeletal maturity at diagnosis	Percentage	79.6%	25.5%	$p < 0.0001$
Athyreotic gland	Percentage	42.9%	18.9%	$p = 0.0016$
Therapy onset days	Median (range)	18 (12-27)	19 (13-27)	n.s.
Initial L-T_4 dose (μg/kg/day)	Median (range)	12.8 (10.6-14.9)	12.5 (10-14.9)	n.s.
TSH normalization time (weeks)	Mean ± SD	4.4±2.3	2.5±1.4	$p < 0.0001$
Mean serum T_4 < 1 year; nmol/L	Mean ± SD	168.8±36.1	172.8±38.2	n.s.
Mean serum T_4 1–2 years; nmol/L	Mean ± SD	159.1±24.7	163.8±26.3	n.s.

* Based on DQ scores of adaptive behavior; ** Parental socioeconomic status; n.s., not significant

dren were divided into 2 subgroups according to the adaptive behavior score (<1SD or ≥ 1SD apart from the mean of control group) (Table 3). There were more females, retarded skeletal maturity, and athyreotic gland cases in the CH group with DQ <1 SD than in the CH group with DQ ≥ 1SD apart from the mean of control group ($p = 0.012$, $p < 0.0001$, and $p = 0.0016$, respectively). The TSH normalization time was longer in the group with DQ <1SD than in the CH group with DQ ≥ 1SD apart from the mean of control group ($p < 0.0001$). There was no statistically significant difference in SES, birth weight, gestational age, day of therapy onset, initial L-T_4 dose, or mean serum T_4 value at 1 or 2 years of age between the two groups (Table 3).

In this study, there were 89 cases that started treatment before 20 days of age and 66 cases that started treatment after 20 days of age. The DQ scores for adaptive behavior, fine motor, gross motor, language, and personal-social behavior were comparable between the patients who began therapy ≤ 20 days after birth and those who began therapy > 20 days after birth ($p > 0.05$). The DQ scores for adaptive behavior, fine motor, gross motor, language, and personal-social behavior aspects of patients in 79 cases who had an initial L-T_4 dose of 10-12.5 μg/kg/day were similar to those in 76 cases who had an initial L-T_4 dose of 12.6-15 μg/kg/day ($p > 0.05$).

Correlative analysis of neurodevelopmental outcomes in CH children at 24 months

The bivariate correlations in Table 4 demonstrate that the pretreatment T_4 concentration, athyreotic gland, and SES correlated with the DQ scores of the five GDS areas. The TSH normalization time was negatively related to the DQ scores of adaptive behavior aspect ($r = -0.348$, $p < 0.01$), but not to the other four aspects. DQ scores correlated with none of the following variables: gender, birth weight, gestational age, day of therapy onset and initial L-T_4 dose. Stepwise selection in the regression analyses revealed that the severity of CH and SES were significant predictors of DQ scores in the five GDS areas; however, TSH normalization time only predicted the adaptive behavior aspect. None of the variables (gender, birth weight, gestational age, day of therapy onset, or initial L-T_4 dose) could predict neurodevelopmental outcome (Table 5).

Table 4 Correlations between characteristics and DQ scores of the CH patients at 24 months of age

	Adaptive behavior	Fine motor	Gross motor	Language	Personal-social behavior
Gender	0.103	0.155	-0.049	0.141	0.029
SES***	0.182*	0.737**	0.231**	0.882**	0.410**
Gestational age	0.041	0.013	-0.08	0.031	-0.024
Birth weight	0.017	0.001	0.024	-0.034	0.094
Athyreotic gland	-0.308**	-0.207**	-0.164*	-0.212**	-0.165*
Serum T_4 at diagnosis	0.417**	0.319**	0.208**	0.308**	0.222**
TSH normalization time	-0.348**	-0.103	-0.122	-0.1	-0.066
Therapy onset days	0.063	-0.091	0.023	-0.067	0.044
Initial L-T_4 dose	0.009	0.051	0.049	0.055	0.015

* Correlation is significant at the 0.05 level (two-tailed); ** Correlation is significant at the 0.01 level (two-tailed).
*** Parental socioeconomic status

Table 5 Multiple regression analyses of CH patients characteristics on DQ scores at 24 months of age

Independent variables*	Adaptive behavior		Fine motor		Gross motor		Language		Personal-social behavior	
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
Serum T_4 at diagnosis	0.182	0.000	0.197	0.000	0.148	0.005	0.214	0.000	0.141	0.001
SES**	0.805	0.017	4.373	0.000	1.681	0.002	5.736	0.000	2.557	0.000
TSH normalization time	-1.692	0.000								
R^2 adjusted	0.276		0.661		0.089		0.894		0.215	
Significance of model	$p = 0.000$		$p = 0.000$		$p = 0.000$		$p = 0.000$		$p = 0.000$	

*Independent variables were included by stepwise selection in the regression analyses; ** Parental socioeconomic status

Discussion

Neonatal screening has become a standard tool in many parts of the world and has been successful in achieving a much improved neurodevelopmental outcome in children with CH. However, a series of follow-up studies on the cohorts who were originally screened revealed that children with CH still had persistent subtle deficits, even if they received early treatment [7, 9]. In a review of 51 published papers comparing intelligence quotient (IQ) outcome in infants with CH to that of sibling or classmate control subjects, 18 found no significant IQ difference, while 33 found a significant difference, with IQ ranging from 5 to 25 points lower in infants with CH [22]. In evaluating important variables, there is evidence that age of treatment onset, starting L-T_4 dose, severity of hypothyroidism, TSH normalization time, and SES each play an important role in neurodevelopmental outcome.

The effect of the age of treatment onset on intellectual development is a matter of contention. In a review of 11 comparative studies, patients starting treatment within 30 days of life had higher IQ than patients who started treatment after 30 days [22]; this result was further confirmed by a French report evaluating mean global IQ [23]. However, an Australian report showed that the mean full scale IQs were similar between infants who started treatment after 14 days of age and those who started before 14 days of age [24]. In this study, the DQ scores of patients who started treatment before 20 days and those who started after 20 days were similar at 24 months of age: no correlation was found between the starting day of treatment and DQ scores if treatment was begun within one month of birth. Apparently, this further advancement in age of treatment onset did not further improve intellectual development. It does appear to be important to detect most cases and start treatment within one month of birth based on reports [19, 20].

Recent reports about L-T_4 starting dose gave contradictory results [2, 3]. In a review of ten studies that examined the effects of different starting L-T_4 doses on psychometric outcome, two reported no effect, six reported a higher IQ with higher starting doses, and another two reported a higher IQ with lower starting doses [22]. Furthermore, an additional study did not find a correlation between the initial L-T_4 dose and outcome [25]. In this study, we used the recommended L-T_4 dose of 10-15 μg/kg/day, and found the DQ scores of patients with an initial L-T_4 dose of 10-12.5 μg/kg /

day were comparable to those with an initial L-T_4 starting dose of 12.6-15 μg/kg/day. There is no correlation between initial L-T_4 dose (range, 10-15 μg/kg/day) and DQ scores. To what extent the initial L-T_4 dose is a key factor in preserving optimal brain development in CH patients is unclear [26]. The currently recommended L-T_4 dose of 10-15 μg/kg/day appears to achieve the best IQ outcome [3].

Severity of CH correlated significantly with mental development with a median therapy onset age of 28 days [7]. A report showed that infants with severe hypothyroidism had lower IQ than a group with moderate hypothyroidism ($p < 0.05$) [3]. These studies indicate that brain injury in severe CH might have accrued in the prenatal period. It is known that maternal hypothyroidism during pregnancy can result in cognitive and motor deficits in offspring [27]. CH is already expressed in fetal life, as maternal T_4, transferred *via* the placenta, is insufficient to fill the gap in fetal T_4 production; therefore, the observed deficits might also be a consequence of the prenatal hypothyroid state. Severity of CH was an important predictor of long-term outcome [7].

TSH normalization time is inversely related to neurodevelopmental outcome [28]. CH children whose TSH normalization time was more than 3 months have demonstrated significant abnormalities in postural, educational, and psychomotor aptitudes in comparison with those who experienced TSH normalization before 3 months of age and control children [29]. In our study, the TSH normalization time was correlated with the DQ score of adaptive behavior. The serum TSH should become normal in most infants after one month of treatment. In some cases, a high TSH (10-20 mIU/L) may persist despite a normal serum T_4 or vice versa [16], usually because of undertreatment or noncompliance. Therefore, it is important to closely monitor these infants and adjust their L-T_4 dose accordingly until the desired TSH level is achieved. Normal serum TSH is essential for the normal development of the neurosensorial afferent pathways (vestibular, proprioceptive) as well as areas of central integration (cerebellum, vestibular nuclei).

SES is an independent predictor of intellectual outcome in normal and at-risk populations, and has also been reported for children with CH [30]. Children from families with lower SES may be more vulnerable because of suboptimal environmental input compared with children from a more stimulating social environment. Children from families with high SES typically have easy access to a wide range of resources that promote and support their development. Therefore, close surveillance, early detection of developmental delay, and intervention programs are particularly important for the children with CH who are also from families with lower SES.

In summary, newborns with CH may appear to have neurodevelopmental deficits even if they are treated early. The risk factors for neurodevelopmental deficits include the severity of hypothyroidism, late (> 4 weeks) normalization of TSH, and lower SES.

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