Clinical Pediatrics
Volume 46 Number 1
January 2007 53-58

10.1177/0009922806289326
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Mental Development of Infants With Congenital Hypothyroidism: A Longitudinal Study

Makiko Nakamizo, MD,[1] Shin-ichi Toyabe, MD, PhD,[1,2]
Tadashi Asami, MD, PhD,[3] Kouhei Akazawa, PhD[1]

The purpose of this study was to assess the relationship between the clinical findings before starting treatment and the development quotient in children treated for congenital hypothyroidism. Patients with congenital hypothyroidism (n = 129) were divided into favorable and unfavorable groups according to intellectual performance. Children with congenital hypothyroidism generally have a similar intellectual outcome to that of healthy children. However, a low birth weight, the presence of complications, and a high serum thyroid-stimulating hormone value are the risk factors for unfavorable cases, who consistently have a development quotient score of less than 100.

Keywords: congenital hypothyroidism; thyroid-stimulating hormone; developmental quotient score

Introduction

Congenital hypothyroidism (CH) is the most common congenital endocrine disorder. Because thyroid hormone plays an important role in the development and maturation of the central nervous system, children with untreated CH can develop mental retardation. Neonatal screening for CH has been introduced to prevent mental retardation by diagnosing the disease as quickly as possible and thereby initiating thyroid hormone replacement therapy in a timely manner. With the advent of neonatal screening programs for the detection of CH, the prognosis for affected infants has thus been dramatically improving.[1] Despite the sophisticated screening and treatment, however, some patients still do not have a good prognosis.

From the [1]Department of Medical Informatics, Niigata University Medical and Dental Hospital, [2]Division of Pediatrics, Department of Homeostatic Regulation and Development, Niigata Graduate School of Medical and Dental Sciences, Niigata University, and [3]Department of Nursing, Niigata Seiryo University, Niigata City, Japan.

Address correspondence to: Kouhei Akazawa, PhD, Department of Medical Informatics, Niigata University Medical and Dental Hospital, Niigata University, 1-754 Asahimachi-dori, Niigata City, 951-8520, Japan.

Many studies have investigated the determinants in the prognosis and for predicting mental development in patients with CH. The age at the start of therapy had already been demonstrated to be a determinant in the prognosis before neonatal screening began.[2] Some previous studies have reported a positive correlation between mental development and the age at the start of therapy in children with CH after the introduction of a neonatal screening program.[3-5] However, other studies have reported the intellectual outcome (prognosis) to not be correlated with the age at the onset of treatment.[6-8] Additional studies have suggested other determinants related to the prognosis to be the severity of hypothyroidism,[9-11] an insufficient initial dose of l-thyroxine,[4,12] poor compliance with the therapy, and other associated defects or complications.[4] In those studies, the determinants for the intellectual outcome (prognosis) of children with CH were evaluated at either 1 age point or at a few age points.[13-18]

In this study, we evaluated the longitudinal development of intellectual performance in patients with CH by examining the mental development over multiple points of time. The main objective of our study was to investigate the determinants in the mental development of each child with CH.

Table 1. Problems in the Prenatal Period and the Number of Patients

Problems	Patients (n)
During pregnancy	
Toxemia during pregnancy	3
Maternal smoking during pregnancy	3
Maternal thyroid disorder	2
Polyhydramnios	1
Oligoamnios	1
Fetal distress	1
Operation of mother's right ovarium (15th week of pregnancy)	1

Table 2. List of Other Complications Reported by 10 Patients

Complication	Patents (n)
1. Unfavorable environmental circumstances	7
Maternal psychiatric disorder	1
Long-term immobilization/hospitalization	6
Club feet	1
Double outlet right ventricle	1
Surgical treatment for ventricular septal defect	1
Meningitis, sepsis, and bronchitis	1
Epidural hematoma and inguinal hernia	1
Renal tubular dysfunction	1
2. Congenital malformation, others	9
Down syndrome	5
Asphyxia of the newborn	2
Bilateral aberration of clavicles and ankyloglossia	1
Hydrocele, undescended testis, and internal strabismus	1

Methods

Patients and Procedure

The data used in this study were obtained from 129 children with CH who were born from December 1986 to December 2002. The serum levels of thyroid-stimulating hormone (TSH) in the neonates at the fourth to sixth day after birth were screened by using a method of collecting blood spot samples on filter paper and the enzyme-linked immunoabsorbent assay technique. CH was suspected in neonatal screening when the serum TSH levels exceeded the 97th percentile of the assay (about 8 mU/mL).

After further evaluation (TSH, free T4, and major clinical symptoms) and analyses by specialists, the CH patients were treated with L-thyroxine at the Department of Pediatrics of Niigata University Medical Hospital. Informed consent was obtained from the parents of the patients when they first visited our hospital. A clinical and biochemical follow-up was scheduled every 2 months after the start of treatment and then up to 12 months of age. The follow-up for patients older than 1 year was done every 3 months.

The developmental quotient (DQ) was evaluated from 4 to 13 times (mean ± SD, 7.2 ± 2.1) during the observation period for each patient. The dose of L-thyroxine was controlled to maintain the levels of serum TSH within the normal range.

Variables for the determinants of mental development include the following 11 factors: gestational age, birth weight, age at start of therapy, the serum TSH level at diagnosis, the serum free T4 level at diagnosis, first dose L-thyroxine, sex, major clinical symptoms, problems in the prenatal period, a family history of siblings with thyroid disease, and other complications. Major clinical symptoms included prolonged jaundice, edema, large posterior fontanel, goiter, decreased activity, failure to thrive, a hoarse cry, cold hands and feet, constipation, an umbilical hernia, macroglossia, and dry skin. The typically expected problems in such cases were demonstrated by 12 of the 129 patients during the prenatal period and are presented in Table 1. Ten patients had other complications, such as unfavorable environmental circumstances and congenital malformations (Table 2).

Measurement of the Development Quotient

The children, aged 3 months to 3 years, were tested using the revised Gesell Developmental Inventory (the Tsumori-Inage test), a standardized developmental test widely used in Japan.[19-21] The test has a standard value of 100. The patients' mothers filled in the evaluation sheets of the Tsumori-Inage test. The scores were transformed to standard scores based on a comparative reference[21,22] to convert the scores written by the mothers into ones evaluated by the doctors.

Statistical Analyses

We evaluated the time-series DQ scores of the CH children using 3 distinct methods. First, we compared a line graph of the average of 129 children's DQ at every month from 3 to 36 with a standard value of 100. A statistical analysis was performed

Table 3. Characteristics of the Patients

Characteristics	Overall (n = 129)	Group 1-A (n = 12)	Group 1-B (n = 117)	*P*	Group 2-A (n = 54)	Group 2-B (n = 75)	*P*
Gestational age (weeks)	40 (39, 41)	38 (37, 41)	40 (39, 40)	0.307[a]	40 (38, 41)	40 (39, 41)	.278[a]
Birth weight (g)	3070 (2744, 3330)	2365 (2256, 3300)	3080 (2812, 3340)	0.010[a]	2896 (2540, 3250)	3165 (2880, 3460)	.006[a]
Age at start of therapy (days)	31 (24, 40)	45 (38, 79)	31 (23, 38)	0.006[a]	33 (23, 43)	31 (24, 38)	.426[a]
Serum TSH at diagnosis (mU/mL)	15.8 (9.0, 41.8)	16.2 (11.8, 121.3)	15.8 (9.0, 40.01)	0.427[a]	17.5 (10.6, 66.6)	14.2 (8.2, 30.1)	0.107[a]
Serum fT4 at diagnosis (ng/dl)	1.3 (1.0, 1.5)	1.2 (0.6, 1.3)	1.3 (1.0, 1.5)	.062[a]	1.2 (0.8, 1.4)	1.4 (1.2, 1.5)	0.011[a]
First dose L-thyroxine (mg/kg)	9.1 (5.9, 10.5)	9.7 (5.4, 10.8)	8.8 (5.9, 10.3)	.700[a]	8.8 (5.5, 10.7)	9.1 (6.0, 10.2)	0.879[a]
Major clinical symptoms	0 (0, 1)	1 (1, 1)	0 (0, 1)	.066[a]	1 (0, 1)	0 (0, 1)	.017[a]
Female/male	80/49	8/4	72/45	1.000[b]	31/23	49/26	.366[b]
Number of patients with problems in prenatal period	12	3	9	.084[b]	8	4	0.121[b]
Number of patients having siblings with CH	8	0	8	1.000[b]	1	7	.138[b]
Complications	16	7	9	<.001[b]	12	4	.006[b]

Group 1-A patients constantly had a DQ score that lower than 100. Group 1-B patients that did not belong to group 1-A. Group 2-A patients had an average DQ score lower than 100. Group 2-B patients that did not belong to group 2-A. Values in parenthesis are medians (25%, 75%).
a. Wilcoxon rank sum test.
b. Fisher exact probability test.

with a one-way analysis of covariance of the BMDP (Statistical Solutions, Saugus, Mass).

Second, we divided the patients into 2 groups, depending on whether they constantly showed an abnormal DQ score. Group 1-A consisted of 12 patients who constantly had a DQ score of less than 100. Group 1-B consisted of 117 patients that did not belong to group 1-A. A multiple logistic regression analysis was performed to select the risk factors related to group 1-A.

Third, we divided the patients into 2 groups by their average DQ score. Group 2-A consisted of 54 patients with an average DQ score from 3 to 36 months of age of lower than 100. Group 2-B consisted of 75 patients that did not belong to Group 2-A. A multiple logistic regression analysis was performed to select the risk factors related to Group 2-A.

The latter 2 analyses were run on the SPSS 12.0 software package (SPSS Inc, Chicago, Ill) for Windows (Microsoft Corp, Redmond, Wash).[23]

Results

Characteristics of the Patients

The characteristics of the 129 patients (80 girls and 49 boys) are summarized in Table 3. The birth weight was significantly lower in the group having low DQ scores than in the group having high DQ scores (Wilcoxon rank sum test, $P < .05$). Complications were significantly more frequently observed in the patients with low DQ scores than in those with high DQ scores (Fisher exact probability test, $P < .01$). The median ages at the start of therapy in group 1-A and group 1-B were 45 days and 31 days, respectively. The age distributions were significantly different between group 1-A and group 1-B. In addition, the serum-free T4 level at diagnosis was significantly lower in group 2-A than in group 2-B, and major clinical symptoms were significantly more frequently observed in group 2-A than in group 2-B.

DQ Score Comparison Between CH Patients and Healthy Children

The average DQ score of the patients with 129 CH in the period was 100.3. A significance test of the difference between the 2 lines by an analysis of covariance showed this DQ score did not differ from the standard value of 100 ($P = .745$). The null hypothesis that the slope of the average DQ graph is zero was not rejected based on a significance test for slope = 0 by an analysis of covariance ($P = .540$). This showed that the DQ of the patients

Table 4. Probability of Improving the Prognosis of Mental Development With Congenital Hypothyroidism by a Neonatal Screening Program and Thyroid Hormone Replacement Therapy

Group 1- A and 1-B			
Probability	Group 1-A	Group 1-B	Total
≥ 0.06	12	20	32
< 0.06	0	97	97
Total	12	117	129

Sensitivity = 1.00
Specificity = 0.83

Predicted value = 0.84

Group 2-A and 2-B			
Probability	Group 2-A	Group 2-B	Total
≥ 0.5	27	12	39
< 0.5	27	63	90
Total	54	75	129

Sensitivity = 0.50
Specificity = 0.84
Predicted value = 0.70

with CH did not increase or decrease during the treatment.

Multiple Logistic Regression Analysis for Group 1-A and 1-B

A multiple logistic regression analysis was performed to identify the risk factors related to group 1-A. As a result, the factors for group 1-A were the birth weight (estimated regression coefficient, –2.909; standard error, 0.884), complications (estimated regression coefficient, 1.797; standard error, 0.508) and the serum TSH level at diagnosis (estimated regression coefficient, 0.002; standard error, 0.001) using the forward stepwise method.

A Multiple Logistic Regression Analysis for Group 2-A and 2-B

A multiple logistic regression analysis was performed to select the risk factors for group 2-A. As a result, the factors for group 2-A were the birth weight (estimated regression coefficient, –1.112; standard error, 0.573), complications (estimated regression coefficient, 1.126; standard error, 0.439), and the serum TSH level at diagnosis (estimated regression coefficient, 0.002; standard error, 0.001) based on the forward stepwise method.

Sensitivity, Specificity, and Predicted Value

The sensitivity, specificity, and predicted value based on these logistic regression models are summarized in Table 4. The cutoff points of probability for maximizing sensitivity and specificity were set to 0.06 and 0.5 for the 2 analyses, respectively. The estimated sensitivities for group1-A and group 2-A were 1.0 and 0.5, which were thus found to show a substantial difference. The estimated specificities for group1-A and group 2-A were 0.83 and 0.84.

Discussion

This study evaluated the longitudinal trends of intellectual development for children with CH compared with the reference values of the DQ scores for healthy children. Children with CH, on average, maintained an equivalent level of intellectual development with that of healthy children. However, a multiple logistic regression analysis showed a low birth weight, the presence of complications, and a high serum TSH level to be risk factors for unfavorable cases, who constantly had a DQ score of less than 100 during the follow-up period.

Our method for evaluating the intellectual development of the patients was quite unique in that we repeatedly assessed the patients' neurodevelopment, namely an average of 7.2 times. This approach provides a stable trend graph of the monthly average and a reliable appraisal of the risk factors for a poor prognosis compared with other studies. In fact, in related studies, the intellectual development was assessed by a cross-sectional design or only a few times during the patient's course.[10,24,25]

As expected, a multiple logistic regression model based on the previously mentioned 3 risk factors for predicting children with a DQ score of less than 100 during the overall follow-up period demonstrated a 100% sensitivity, thereby satisfying the specificity to predict a poor prognosis in a child's intellectual development. However, the application of the average longitudinal DQ scores for each child to the intellectual outcome provided only a limited sensitivity. The difference in these results suggests that the latter should not be applied to the end point of intellectual development during the follow-up in this study.

Three factors, namely, a low birth weight, comorbidity, and high serum TSH levels at diagnosis were found to be significant factors for predicting a poor prognosis for intellectual development. A low birth weight and the existence of comorbidity might influence the intellectual development of patients, independent of an abnormal thyroid function.

Previous studies have suggested a delay in the start of treatment to be a major factor affecting the intellectual prognosis of the patients.[3,26] Our results were quite different from those of previous studies and clearly showed the patient background to play a bigger role in the intellectual prognosis than the timing of treatment. The reason for this discrepancy is that almost all Japanese pediatricians should uniformly start the treatment as soon as the children show a positive result in mass screening, irrespective of a confirmed diagnosis of CH.

Conclusions

Many recent studies have suggested not only the severity of hypothyroidism but also nonoptimal treatment to play a role in the mental retardation of these patients. A positive association between a high level of treatment, primarily treatment during the first year, and later intelligence has been found in most studies.[27] Therefore, it might be necessary to treat these high-risk patients with higher doses of thyroid hormone.[16,28,29] Because negative associations between high-dose treatment and outcome have been reported,[30] close observations are essential in patients treated with high-dose therapy. The number of clinic visits during the first year of life has been reported to significantly affect the intellectual development of these patients.[31] Frequent monitoring of the thyroid function is also necessary for these high-risk patients.

Acknowledgement

We are grateful to Dr Brian Quinn, Associate Professor in Kyushu University, for help in English proofreading the manuscript.

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