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Original Article

Effects of low-dose levothyroxine on atrial natriuretic peptide and c-type natriuretic peptide in children with neonatal hypothyroidism

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Abstract: Objective: This study was designed to explore the effects of low-dose levothyroxine (LT4) on levels of atrial natriuretic peptide (ANP) and c-type natriuretic peptide (CNP) in neonates with hypothyroidism (NH). Methods: In this retrospective study, a total of 90 cases of NH screened out and confirmed by the First Affiliated Hospital of Zhejiang Chinese Medical University from October 2014 to February 2018 were selected as a study group. 80 healthy children who underwent physical examination during the same time period were enrolled as controls. Before and after treatment with LT4, the changes in the levels of serum thyroid stimulating hormone (TSH) and free thyroxine (FT_4) were observed, and the changes in the levels of ANP and CNP and their relationships to clinical efficacy were evaluated. Additionally, the growth and development of body and the scores of the China-Wechsler Younger Children Scale of Intelligence (C-WYCSI) were compared before and after the treatment, and the changes in the cardiac functions of children in the study group were evaluated. Independent risk factors for mental abnormality after treatment were analyzed by logistic regression. Results: After treatment, TSH levels in patients declined, while the levels of T_3, T_4, free triiodothyronine (FT_3), and FT_4 increased, without significant differences between groups. After treatment, ANP levels in patients increased but CNP levels decreased. ANP levels were negatively correlated with clinical efficacy, but CNP levels were positively correlated with it. Ultrasonic cardiography showed the improved cardiac functions. After treatment, the growth and development of body and the C-WYCSI scores increased compared to those before treatment. First visit date, T_3, FT_4, TSH were independent risk factors for mental disorders in children. Conclusion: For children with NH, low-dose LT4 can correct the level of thyroid function, promote physical and mental development, and improve the levels of ANP and CNP.

Keywords: LT4, neonatal hypothyroidism, atrial natriuretic peptide, c-type natriuretic peptide

Introduction

Neonatal hypothyroidism (NH) refers to a syndrome with malformation of the thyroid and the production of thyroid stimulating hormone (TSH). The former refers to abnormal thyroid development, while the latter is due to the defects in the molecular pathway of forming thyroid hormones (THs) that prevents the intact gland from producing the hormones. Therefore, neonates with NH will develop irreversible neurological impairment and long-term metabolic complications if they are not treated early [1, 2]. The total incidence of NH in every 10,000 liveborn infants is 4.1% according to statistics [3], and it is of crucial importance to conduct neonatal screening in Chinese residents.

The family of natriuretic peptides (NPs) consists of three hormones with distinct characteristics: Atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and c-type natriuretic peptide (CNP), which are primarily related to maintaining cardiac-renal homeostasis. ANP and BNP are primarily synthesized in the heart and less synthesized in other organs, while CNP is mainly produced by endothelial cells [4]. Reportedly, serum peptides change with different thyroid functions. Serum BNP obviously increases in patients with hypothyroidism. THs directly increase ABP expression and regulate the synthesis of ABP and BNP, which is manifested as the increase in mRNA contents in cells. TSH and BNP are significantly high in patients with subclinical hypothyroidism (SH), and the inci-

dence and the mortality rate of cardiac events in the patients are much higher than those in individuals with a normal thyroid [5]. As the most common endocrine disease among neonates, primary congenital hypothyroidism (PCH) needs timely diagnosis and treatment with levothyroxine (LT4) to prevent the irreversible retardation of neurological development [6]. According to Martins et al. [7], SH is related to the overall damage of left ventricular diastolic and systolic functions. Although the course of LT4 treatment is long, it can completely reverse SH, and its replacement therapy positively impacts the cardiac functions of middle-aged women with SH. Currently, the optimal treatment method for children with SH depends on its causes and the degree of elevation of TSH, which should be adjusted according to specific conditions. In the case of delayed or improper treatment with LT4, obvious hypothyroidism will increase the risk of mental illness in children, and aggravate their growth retardation, metabolic disorders, and injuries. Moreover, SH is related to an increased risk of cardiovascular diseases and adverse outcomes (such as atherosclerosis and related cardiovascular events). Total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) can be decreased after treatment with LT4 [8, 9]. Therefore, we suspect that the treatment with LT4 may affect ANP and CNP in children with hypothyroidism. However, there are currently few reports on the expression of CNP in children with NH.

Therefore, in this study, the effects of LT4 on the levels of ANP and CNP in NH were explored, and the therapeutic effects of this drug were also investigated, with the purpose of providing more experimental data for clinical practice.

Materials and methods

Research subjects

In this retrospective study, a total of 90 cases of NH neonates treated in the First Affiliated Hospital of Zhejiang Chinese Medical University from October 2014 to February 2018 were selected as the study group, including 56 males and 34 females with an average gestational age of (39.2±1.0) weeks (range: 37-41 weeks). Totally 80 healthy newborns who underwent physical examination during the same time period were enrolled, including 53 males and 27 females, with an average gestational age of (39.3±1.2) weeks (range: 37-42 weeks).

Inclusion criteria: neonates with delayed jaundice regression, large anterior and posterior fontanelles, less crying and umbilical hernia; neonates with increased TSH and complicated with reducing free thyroxine (FT_4). Exclusion criteria: neonates with complications such as congenital malformation, severe infection, hypoxic-ischemic encephalopathy, asphyxia after birth and intracranial hemorrhage; neonates who have serious conditions of other organ systems (including multiple malformations, cyanotic congenital heart disease, neonatal necrotizing enterocolitis, neonatal septicemia and bilirubin encephalopathy). In this study, the family members of the children signed the informed consent form, and this study was approved by the Ethics Committee of First Affiliated Hospital of Zhejiang Chinese Medical University (IRB-20140915).

Outcome measures

Before and after the treatment with LT4, the changes in the serum TSH and FT_4 levels in the study group were observed. The changes in the levels of ANP and CNP and their correlations with clinical efficacy in the study group were analyzed. The growth and development of body and the scores of the China-Wechsler Younger Children Scale of Intelligence (C-WYCSI) were compared. The changes in the cardiac functions of children in the study group were evaluated.

Detection methods

Thyroxine levels: After all neonates were fully fed for 72 hours, their peripheral blood was collected from the lateral heel, and the blood was dripped on Schleicher903 filter papers. Three samples were collected, and the formation of blood spots (with a diameter of more than 8 mlTl) permeating both sides of the filter papers was ensured. After natural drying, the spots were packed and sealed with plastic bags, and then stored at a constant temperature of 4°C. The time-resolved fluorescence immunoassay analyzer and its related matching reagents from PerkinElmer Inc, Finland were used for screening. Time-resolved fluoroimmunoassay was performed to track suspected children with the TSH cut-off value > 9 mUlml in their blood spots. Venous blood was extracted from the suspected neonates to detect the levels of T_3, T_4, serum free triiodothyronine (FT_3), serum FT_4, and TSH using chemiluminescence immu-

noassay. The chemiluminescence immunoassay analyzer and its related matching reagents from Roche Pharmaceutical Co., Ltd. were used for detection.

Detection of ANP and BNP levels: Fasting venous blood (2 mL) was extracted from each child in the morning. The blood was detected by enzyme-linked immunosorbent assay (ELISA) with the BIO-TEK ELx800 microplate reader.

Ultrasonography

A Vivid7 (Vivid7, GE, Horten, Norway) Color Doppler Ultrasonic Diagnosis Apparatus was applied, with a transducer frequency of 5-8 mHz. All ultrasound parameters were detected for three consecutive cardiac cycles to acquire the average value. First, left ventricular ejection fraction (LVEF), left ventricular fractional shortening (LVFS), left atrial diameter (LA), and aortic diameter (AO) were measured on the M-mode echocardiography, and LA/AO was calculated. Then, the blood flow spectrum of pulse-wave Doppler (PWD) at the mitral orifice was recorded routinely on the apical four-chamber section. The early diastolic peak flow velocity (E) and the late diastolic peak flow velocity (A) were measured, so as to calculate the E/A value. All examinations were carried out with babies in a quiet and horizontal position.

Therapeutic methods

The children were given basic nursing and kept warm. Children in the study group were administrated with 10 ug/kg levothyroxine sodium (Euthyrox, H20140052) at least 30 minutes before the first meal, once a day [10]. After their related indices returned to normal, the medication was gradually reduced until the drug was discontinued. The medication was given for 3 consecutive weeks.

Efficacy evaluation

The efficacy was assessed according to the children's clinical symptoms and the changes in the indices of thyroid functions. Markedly effective: after treatment, the clinical symptoms disappeared and the levels of FT_4, FT_3 and TSH returned to normal. Effective: after treatment, the clinical symptoms were relieved obviously and the levels of the indices were close to normal. Ineffective: after treatment, the clinical symptoms were not relieved and the levels of the indices had no change. The total effective rate was the sum of the rates of markedly effective and effective.

Adverse reactions

Whether children in the study group suffered from weight loss or complicated insomnia was evaluated.

Physical and mental growth and development

Before and 6 months after treatment, the body length, body mass and head circumference of children in the study group were evaluated and recorded. At the age of 2, the verbal intelligence quotient (VIQ), performance intelligence quotient (PIQ) and full intelligence quotient (FIQ) of children in both groups were measured using the China-Wechsler Younger Children Scale of Intelligence (C-WYCSI), which covers dimensions of PIQ, VIQ and FIQ3, and its score was evaluated by psychological testing professionals. After the evaluation, the scores of each subscale were input into the computer to obtain the test scores of each subscale, in which the FIQ score ≥ 85 was regarded as normal intelligence; the total FIQ score between 70-84 points was regarded as the critical level, and FIQ < 70 was regarded as mental retardation [11].

Statistical methods

SPSS 19.0 (Asia Analytics Formerly SPSS China) was used for data analysis. Counted data were expressed as rate and compared by a χ^2 test. Measured data were expressed as mean ± SD. The Independent t test was used for comparison between the two groups, and paired t test was used for comparison in the same group before and after treatment. Pearson correlation was used to analyze the pairs of measured data. $P < 0.05$ was considered a significant difference.

Results

Comparison of general information

The general information and the clinical manifestations of children in the study group were as shown, and there was no significant difference in sex and age between the control group and the study group (**Table 1**).

Table 1. General information

Factor	Study group (n=90)	Control group (n=80)	t/χ^2	P
Gender			0.299	0.585
Male	56 (62.22%)	53 (66.25%)		
Female	34 (37.78%)	27 (33.75%)		
Gestational age (week)	39.2±1.0	39.3±1.2	0.592	0.554
First visit date (day)	18.6±8.3			
Clinical manifestations				
Delayed neonatal jaundice	34 (37.78%)			
Increasing anterior fontanelle	30 (33.33%)			
Unclosed posterior fontanelle	13 (14.44%)			
Umbilical hernia	12 (13.33%)			
Less crying	32 (35.56%)			

Note: Clinical manifestations cover multiple symptoms.

Comparison of levels of THs before and after treatment

At one month after treatment, serum TSH levels were reduced, but the levels of T_3, T_4, FT_3 and FT_4 rose in the study group, and there was no significant difference in T_3, T_4, FT_3, FT_4 or TSH between the study group and the control group, as shown in **Figure 1** ($P > 0.05$).

Comparison of ANP and CNP levels before and after treatment and their relationships to clinical efficacy

After the treatment with LT4, there were 65 cases that were markedly effective, 22 effective, and 3 ineffective, showing a total effective rate of 96.67%. At one month after treatment, serum CNP levels in the study group declined ($P < 0.05$), while ANP levels increased ($P < 0.05$). ANP levels were negatively correlated with efficacy ($r=-0.531$), while CNP levels were positively correlated with efficacy ($r=0.717$) (both $P < 0.05$) (**Figure 2**).

Comparison of growth and development and C-WYCSI scores before and after treatment

At 6 months after treatment, the growth and development of body was better than that before treatment; at 2 years after treatment, the C-WYCSI scores were better than those before treatment ($P < 0.05$) (**Table 2**).

Comparison of cardiac function before and after treatment

According to the traditional M-mode echocardiography, LA was not significantly different before and after treatment ($P > 0.05$), but the differences in AO, LA/AO, LVEF and LVFS were statistically significant (all $P < 0.05$). According to the PWD at mitral orifice, after treatment, the E value and the E/A value were both higher than those before treatment ($P < 0.05$), but the A value was not statistically different before and after treatment ($P > 0.05$).

Comparison of adverse reactions

With respect to adverse reactions, there were 2 cases of weight loss and 4 cases of insomnia complicated with weight loss, showing an incidence of adverse reactions of 6.7% (**Table 3**).

Analysis of risk factors for abnormal intelligence after treatment

According to the FIQ detected at the age of 2, all the children were re-divided into a normal intelligence group ($FIQ \geq 85$) and an abnormal intelligence group ($FIQ < 85$). In comparing the clinical data of the two groups, significant differences were found in first visit date, T_3, FT_3, FT_4, T_4, and TSH between the two groups (**Table 4**). We performed logistic regression analysis on the indicators with a statistical difference in the univariate analysis. The results showed that first visit date, T_3, FT_4, and TSH were independent risk factors for abnormal intelligence in children (**Table 5**).

Discussion

Neonatal hypothyroidism (NH) indicates the lack of THs at birth, which triggers serious mental and growth retardation if it is not diagnosed and treated in time [12]. As a reliable and commonly used prescription drug for treating thyroid diseases, LT4 is adopted to alleviate the symptoms and signs of hypothyroidism and maintain the concentration of TSH within its normal range. Delayed recognition of SH and hyperthyroidism will negatively affect the cardiovascular system [13, 14].

In the present study, we primarily discussed the effects of LT4 on ANP and CNP levels in children with NH, and explored the changes in the indi-

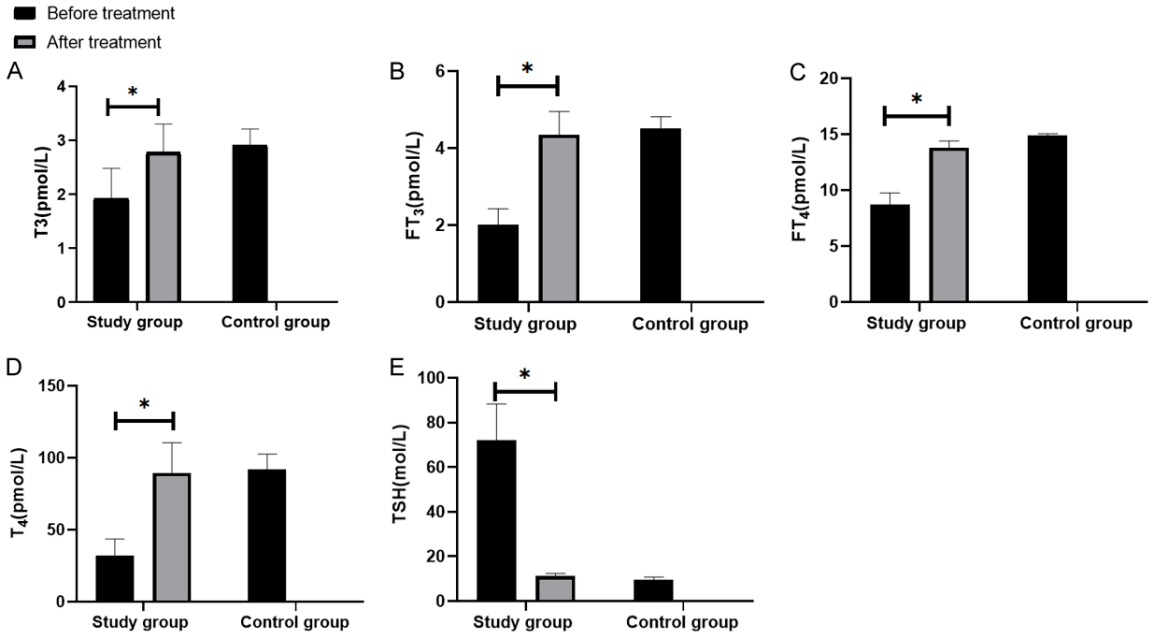

Figure 1. Comparison of levels of THs before and after treatment. A-E: After treatment, T_3, T_4, FT_3, and FT_4 in the study group increased significantly ($P < 0.05$), and were not greatly different from the control group ($P > 0.05$), while TSH decreased significantly and had no significant difference compared to the control group. * indicates $P < 0.05$. free triiodothyronine (FT3), thyroid stimulating hormone (TSH).

ces of thyroid function. The purpose of LT4 replacement therapy is to correct hypothyroidism and ensure the normal growth and neuropsychological development of children. According to prior research, the treatment of children who were diagnosed with early NH by screening programs must be maintained until the age of 3 years without interruption, so as to ensure normal thyroid function. The treatment should be also maintained until their brain is fully developed to prevent mental retardation; children with NH who have received early and appropriate treatment have a normal intelligence quotient [15, 16]. In the present study, after treatment, TSH levels in patients declined, while the levels of T_3, T_4, FT_3, and FT_4 increased. According to the 6-month follow-up, the growth and development of body and the C-WYCSI scores were significantly improved, and the total effective rate of the children was 96.67%. In some studies, more than half of hypothyroidism patients with high thyroxine levels have impaired left ventricular filling, and the decrease of NT-proANP levels is generally caused by atrial degeneration, which is possibly because of the fact that TH-dependent hemodynamic stress prevents NT-proANP from releasing cells from the heart into circulation [17]. After thyroidectomy, the results of RT-PCR showed that ANF mRNA in the rat heart was lower than that in the control group, which indicates that hypothyroidism is related to a reduction of cardiac function [18]. Some studies have shown that LT4 has a certain influence on abnormal left ventricular diastolic function; short-term LT4 can be used for replacement therapy and reverse the influence [19]. This is consistent with our research results that after treatment, ANP levels were higher than those before treatment and were negatively correlated with the clinical efficacy; the ultrasonography showed that the clinical symptoms were relieved. According to study by Schouten et al., after the thyroid function of children with hyperthyroidism recovers, plasma CNP products are reduced with the increase of growth rates and THs, and the reduction of CNP is closely related to the decrease in THs [20]. At present, there are few reports on CNP and NH. In the present study, after treatment, CNP levels were lower than those before treatment; the levels were reduced with an increase in the therapeutic effect and were positively correlated with its efficacy. Thus, treatment with LT4 can improve ANP and decrease CNP levels in children with NH, correct the levels of thyroid function, and

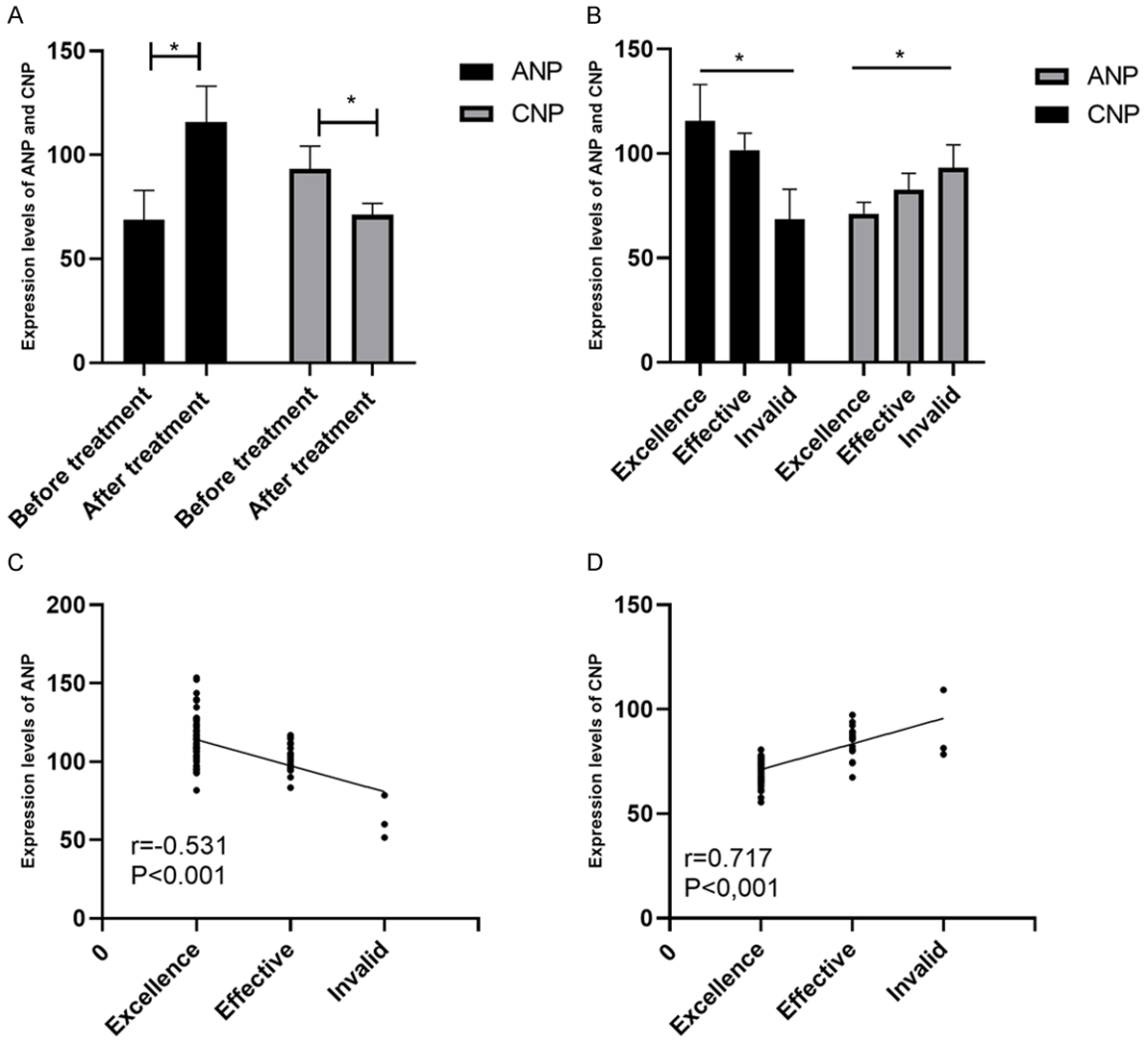

Figure 2. Comparison of ANP and CNP levels before and after treatment and their relationships with clinical efficacy. A: Expression levels of ANP and CNP before and after treatment. B: Expression levels of ANP and CNP in those with different efficacy. C: Relationship between ANP and clinical efficacy. D: Relationship between CNP and clinical efficacy. * indicates $P < 0.05$. Atrial natriuretic peptide (ANP), c-type natriuretic peptide (CNP).

Table 2. C-WYCSI scores before and after treatment

Item	Before treatment	After treatment	t	P
PIQ	91.21±13.12	103.32±14.35	5.909	< 0.001
VIQ	90.25±11.67	102.11±12.86	6.479	< 0.001
FIQ	86.58±13.69	101.59±14.52	7.136	< 0.001
Body length/cm	48.6±2.3	65.4±4.2	33.28	< 0.001
Head circumference/cm	33.7±2.1	43.7±2.4	29.75	< 0.001
Body mass/g	3317.9±268.5	7338.3±485.9	68.70	< 0.001

Note: verbal intelligence quotient (VIQ), performance intelligence quotient (PIQ), full intelligence quotient (FIQ).

promote their physical and mental development. Finally, we conducted a multivariate analysis to explore the independent risk factors for abnormal intelligence after treatment, and found that the first visit date, T_3, FT_4, and TSH were independent risk factors for abnormal intelligence. The results suggest that we should pay attention to the relevant factors to protect the intelligence of children.

There are also some limitations in this study. First, it is difficult to follow up the control group, a healthy population, for the long term, so we can only use the normal indicators of their admission testing for comparison, and

Table 3. Comparison of indices of cardiac functions before and after treatment

Item	Before treatment	After treatment	t	P
M-mode echocardiography				
LA (mm)	10.66±0.75	11.12±1.01	0.318	0.7506
AO (mm)	10.36±0.84	10.01±0.63	3.162	0.0018
LA/AO	1.06±0.05	1.15±0.09	8.293	< 0.001
LVEF (%)	62.23±4.22	67.55±5.34	7.415	< 0.001
LVFS (%)	28.05±4.02	31.11±3.42	5.500	< 0.001
PWD at mitral orifice				
E (cm/s)	57.65±12.01	70.09±8.51	8.018	< 0.001
A (cm/s)	64.63±10.15	63.16±10.03	0.977	0.330
E/A	0.79±0.25	1.13±0.32	7.943	< 0.001

Note: left ventricular ejection fraction (LVEF), left ventricular fractional shortening (LVFS), left atrial diameter (LA), aortic diameter (AO), pulse-wave Doppler (PWD) he early diastolic peak flow velocity (E), the late diastolic peak flow velocity (A).

Table 4. Univariate analysis

	Normal intelligence group (n=69)	Abnormal intelligence group (n=21)	t/χ^2	P
Gender			1.129	0.288
Male	45 (65.22%)	11 (52.38%)		
Female	24 (34.78%)	10 (47.62%)		
Gestational age (week)	39.3±1.0	38.9±0.9	1.641	0.104
First visit date (day)	15.8±6.8	28.1±5.2	7.627	< 0.001
Clinical manifestations				
Delayed neonatal jaundice	24 (34.78%)	10 (47.62%)	1.129	0.288
Increasing anterior fontanelle	22 (31.88%)	8 (38.10%)	0.280	0.597
Unclosed posterior fontanelle	11 (15.94%)	2 (9.52%)	0.537	0.464
Umbilical hernia	8 (11.59%)	3 (14.29%)	0.109	0.742
Less crying	20 (28.99%)	4 (19.05%)	0.813	0.367
T_3 (pmol/L)	1.97±0.44	1.68±0.46	2.617	0.010
FT_3 (pmol/L)	2.58±0.37	2.25±0.50	3.284	0.002
FT_4 (pmol/L)	9.15±1.17	7.94±1.22	4.109	< 0.001
T_4 (pmol/L)	26.06±14.04	17.93±13.28	2.352	0.021
TSH (mu/L)	70.13±18.54	85.54±21.08	3.229	0.002
ANP (pg/ml)	71.01±13.17	65.09±11.96	1.841	0.069
CNP (pg/ml)	91.96±9.44	89.51±11.43	0.990	0.325

Note: free triiodothyronine (FT3), atrial natriuretic peptide (ANP), c-type natriuretic peptide (CNP), thyroid stimulating hormone (TSH).

Table 5. Multivariate analysis

Factor	B	S.E	Wals	Sig.	Exp (B)	95% C.I. of EXP (B)	
						Lower limit	Upper limit
First visit date	-0.284	0.084	11.531	0.001	0.753	0.639	0.887
T_3	2.235	1.048	4.554	0.033	9.350	1.200	72.860
FT_3	1.074	1.178	0.830	0.362	2.926	0.291	29.471
FT_4	0.830	0.382	4.706	0.030	2.292	1.083	4.851
T_4	0.023	0.037	0.369	0.554	1.023	0.951	1.101
TSH	-0.055	0.023	6.010	0.014	0.946	0.905	0.989

Note: free triiodothyronine (FT3), thyroid stimulating hormone (TSH).

it is difficult to collect their FIQ at the age of 2. Secondly, the specific mechanism affecting treatment is not clear, and more basic experiments are required to further support our point of view.

For children with NH, treatment with LT4 can correct the levels of thyroid function, promote physical and mental development, and improve the levels of ANP and CNP. However, after treatment, whether the children will develop long-term lesions of the thyroid or endocrine organs still needs confirmation by multi-center studies.

Disclosure of conflict of interest

None.

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