

Original Article

Predictive value of combined detection of TSH, FT4 and gestational age and relevant factors for congenital hypothyroidism in newborns

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Abstract: Objective: This study aimed to study the predictive value of combined detection of TSH, FT4 and gestational age and analyze the relevant factors for congenital hypothyroidism (CH) in newborns. Methods: 46 neonates with hypothyroidism and 46 healthy neonates were randomly selected as the study group and control group, and serum TSH and FT4 were detected by electrochemical luminescence. The single and combined predictive value of serum TSH, FT4 and gestational age in neonates with hypothyroidism was analyzed, and the logistic regression analysis was used to analyze the influencing factors of neonatal hypothyroidism. Results: Serum TSH in study group was significantly higher than that in control group, serum FT4 and gestational age were significantly lower than those in the control group ($P < 0.05$). The AUC of TSH was slightly higher than that of FT4 and gestational age for detecting CH in newborns, but the sensitivity and AUC of combined detection of TSH, FT4 and gestational age were higher than those of single detection of TSH, FT4 and AUC for CH in newborns ($P < 0.05$). The maternal thyroid abnormality, fetal distress, maternal diabetes, and gestational age < 33 weeks were independent risk factors for CH in newborns ($P < 0.05$). Conclusion: TSH, FT4 and gestational age have higher predictive value for CH in newborns. The combined detection of TSH, FT4 and gestational age has the highest predictive value, which can be applied as one of the optimal screening schemes for CH in newborns. And the maternal thyroid abnormality, fetal distress, maternal diabetes and gestational age < 33 weeks are independent risk factors for CH in newborns. The occurrence of CH in newborns can be avoided by preventing these factors.

Keywords: TSH, FT4, gestational age, congenital hypothyroidism (CH) in newborns, predictive value

Introduction

Congenital hypothyroidism (CH) is a disorder of thyroid hormone synthesis caused by congenital thyroid injury in newborns [1]. The CH in newborns can lead to growth, development and mental retardation. The reason is that thyroid function exerts a key role in the growth and development of newborns, especially in the development of nervous system [2, 3]. However, the CH in newborns is often neglected by parents because its early symptoms are not obvious [4]. Therefore, how to effectively predict and screen CH in the early newborn is of great significance for reducing the number of mentally retarded children and the burden of family and society.

The detection of serum indicators is the main method of clinical screening for CH in newborns

all the time. The thyroid stimulating hormone (TSH) and free thyroxine (FT4) are common indicators for screening CH [5]. Some studies [6] have shown that the serum TSH in the neonates with CH was increased remarkably. Its main detection principle is that the decreased thyroid concentration in blood of children with CH will cause the increased secretion of pituitary TSH, which can be detected by dry blood filter paper [7]. However, some studies have revealed that the change of TSH was not obvious for children with central CH. Therefore, it is necessary to screen CH by combined detection of TSH and FT4 [8]. In recent years, there are more and more studies about the influence of gestational age on the incidence of CH in newborns. Some studies believed that the development of hypothalamus-pituitary-thyroid axis function of preterm infants was not as perfect as that of term infants, which easily led to the

temporary occurrence of low thyroid hormone blood sign. The screening positive rate of TSH of preterm infants might be lower than that of term infants, which was easy to cause misdiagnosis. Other studies [9] clearly suggested that the neonates with lower gestational age are more likely to suffer from CH. The prediction and screening of CH in newborns is only the first step in the treatment of diseases. More importantly, it is necessary to find the high-risk factors affecting the occurrence of diseases and take corresponding measures to prevent the occurrence of diseases.

Therefore, the combined prediction of TSH, FT4 and gestational age for CH in newborns can provide a more accurate screening scheme. The analysis of relevant factors of the disease can provide more theoretical basis for the prevention of CH in newborns.

Materials and methods

General data

From Mar 2016 to Sep 2018, forty-six neonates with CH diagnosed in our hospital were randomly selected as the study group. Among them, 24 were male and 22 were female. The average age of the neonates was 43.24 ± 6.33 days. Forty-six healthy neonates born in our hospital during the same period were selected as the control group. Inclusion criteria: the study group included neonates who met clinical diagnostic criteria for CH in newborns, while the control group included healthy neonates confirmed by comprehensive testing. Exclusion criteria: the neonates who survived less than 10 days; the neonates with other serious organ disorders; the neonates with severe immune system diseases; the neonates whose parents refused to participate in the experiment. All family members of newborns agreed to join the experiment and signed the informed consent. This study has been approved by the Xingtai People's Hospital, Hebei Medical University Ethics Committee.

Examination methods

After 3 days of birth, the venous blood was sampled, and the serum was obtained by centrifugation. The serum TSH (Wuhan Easy Diagnosis Biomedicine Co., Ltd) and FT4 (Henan MaincareBio Co., Ltd) were detected by

chemiluminescence using the Abbott I-2000 machine. Electrochemiluminescence can be divided into test tube reaction and machine detection. In the test tube reaction, antibodies labeled with $[\text{Ru}(\text{bpy})_3]^{2+}$, biotin-combined antibodies and specimens to be tested were added into the test tube. Reaction was performed at 37°C for 10 min, followed by the addition of SA magnetic particles. And then the tubes were incubated at 37°C for 10 min and put into the machine for inspection.

Outcome measures

(1) The serum TSH, FT4 and gestational age of the two groups were compared. (2) The predictive values of single and combined detections of serum TSH, FT4 and gestational age for CH in newborns were analyzed. (3) The single factor analysis was carried out on the factors influencing the occurrence of CH in newborns. (4) The factor related to CH in newborns in the single factor analysis was taken as the independent variable, and the occurrence of CH in newborns was taken as the dependent variable. The factors influencing CH in newborns were analyzed by logistic regression analysis.

Statistical methods

SPSS 19.0 software (Bi Insight (Beijing) Information Technology Co., Ltd.) was utilized for statistical analysis. Chi-square test was utilized to compare the enumeration data. Mean \pm standard deviation was applied to express the measurement data. T test was applied for comparison between the two groups. Logistic regression analysis was applied for multi-factor analysis. $P < 0.05$ indicated that the difference was statistically significant.

Results

General data comparison

There was no remarkable difference in gender, age and birth weight between the two groups ($P > 0.05$), which was comparable (**Table 1**).

Comparison of TSH, FT4 and gestational age between two groups

The TSH, FT4 and gestational age of the study group were 5.31 ± 1.17 mIU/L, 7.39 ± 1.13 pmol/L and 33.61 ± 3.2 weeks respectively.

Predictive value of combined detection of TSH, FT4

Table 1. General data table

Factor	Study group n = 46	Control group n = 46	t/X ²	P
Gender			0.044	0.835
Male	24 (52.17)	25 (54.35)		
Female	22 (47.83)	21 (45.65)		
Age (days)			0.045	0.823
≥ 43	20 (43.48)	19 (41.30)		
< 43	26 (56.52)	27 (58.70)		
Weight (kg)			0.045	0.812
≥ 3.5	27 (58.70)	28 (60.87)		
< 3.5	19 (41.30)	18 (39.13)		
Height (cm)	48.26 ± 3.37	48.27 ± 3.41	0.014	0.989
HR (time/min)	98.61 ± 12.33	97.98 ± 12.05	0.278	0.805
Delivery method			0.050	0.822
Natural childbirth	31 (67.39)	32 (69.57)		
Caesarean section	15 (32.61)	14 (30.43)		
Head circumference (cm)	34.11 ± 2.05	34.09 ± 2.07	0.047	0.963

Table 2. Comparison of TSH, FT4 and gestational age in two groups

Factor	Study group n = 46	Control group n = 46	t/X ²	P
TSH (mIU/L)	5.31 ± 1.17	3.98 ± 0.55	6.977	< 0.001
FT4 (pmol/L)	8.89 ± 1.13	10.23 ± 1.26	5.370	< 0.001
Gestational age (week)	33.61 ± 3.26	36.84 ± 2.55	5.293	< 0.001

Table 3. Predictive values of single and combined detections of TSH, FT4 and gestational age for CH in newborns

Factor	Sensitivity	Specificity	AUC
TSH	82.61%*	73.91%	0.844*
FT4	78.26%*	67.39%	0.793*
Gestational age	76.09%*	71.74%	0.795*
Combined detection	95.75%	67.39%	0.913

Note: *P < 0.05 compared with the combined test.

The TSH, FT4 and gestational age of the control group were 3.98 ± 0.55 mIU/L, 13.23 ± 1.97 pmol/L and 39.84 ± 2.55 weeks respectively. The serum TSH of the study group was higher than that of the control group, and the serum FT4 and gestational age were lower than those of the control group (P < 0.05) (Table 2).

Predictive values of single and combined detections of TSH, FT4 and gestational age for CH in newborns

The sensitivity, specificity and AUC of TSH for the prediction of CH in newborns were 82.61%,

73.91% and 0.844. The sensitivity, specificity and AUC of FT4 for the prediction of CH in newborns were 78.26%, 67.39% and 0.793. The sensitivity, specificity and AUC of gestational age were 76.09%, 71.74% and 0.795. The sensitivity, specificity and AUC of combined detection of TSH, FT4 and gestational age for the prediction of CH in newborns were 95.75%, 95.75% and 0.913. The AUC of TSH was slightly higher than that of FT4 and gestational age for detecting CH in newborns, but the sensitivity and AUC of combined detection of TSH, FT4 and gestational age were higher than those of single detection of TSH, FT4 and AUC for CH in newborns (P < 0.05) (Table 3 and Figure 1).

Single factor analysis for CH in newborns

The gender, age, maternal status and other clinical factors

were included in the analysis. There was no remarkable relationship between the gender, weight and delivery method and CH in newborns (P > 0.05). The maternal thyroid abnormality, fetal distress, gestational age, and maternal diabetes were associated with CH in newborns (P < 0.05) (Table 4).

Multi-factor analysis for CH in newborns

The factors that have obvious correlation with CH in newborns from the single factor analysis were taken as independent variables and assigned (See Table 5). Logistic multi-factor analysis was applied to analyze the factors of CH in newborns. The results revealed that the maternal thyroid abnormality, fetal distress, maternal diabetes, and gestational age < 33 weeks were independent risk factors for CH in newborns (Table 6).

Discussion

CH in newborns is a disease that has a serious impact on the growth and development of newborns, especially for the development of the

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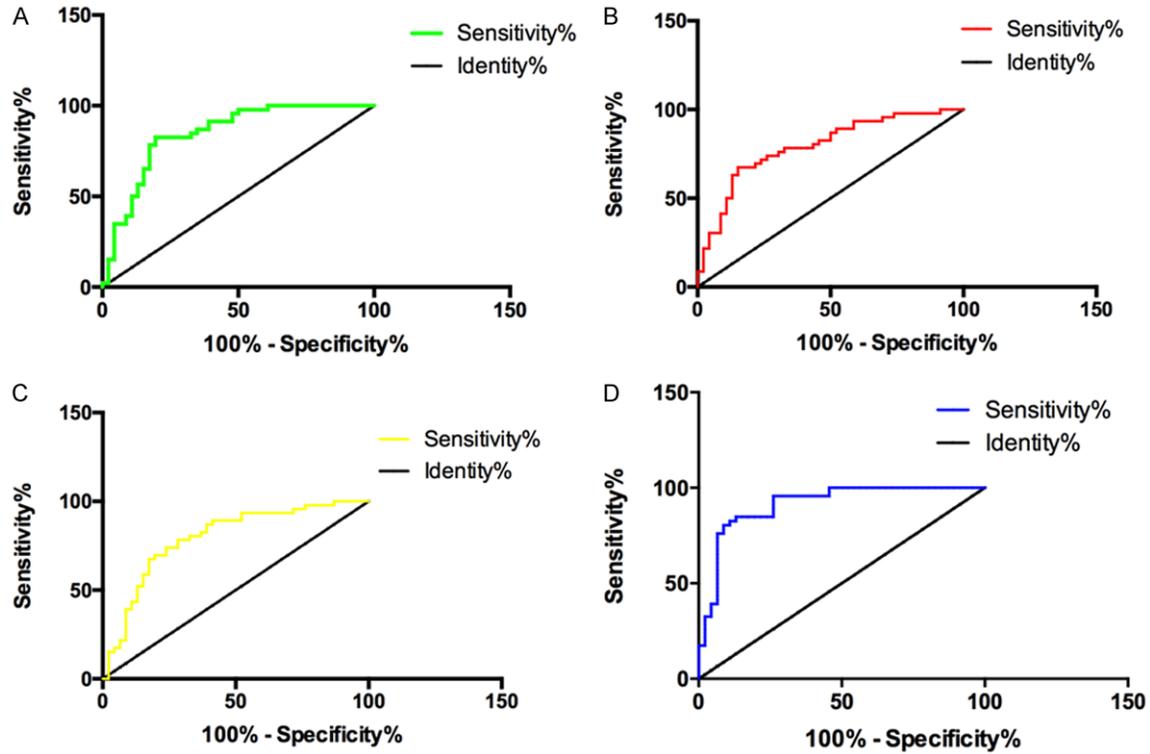


Figure 1. ROC. A. The sensitivity, specificity and AUC of TSH for the prediction of CH in newborns were 82.61%, 73.91% and 0.844. B. The sensitivity, specificity and AUC of FT4 for the prediction of CH in newborns were 78.26%, 67.39% and 0.793. C. The sensitivity, specificity and AUC of gestational age for the prediction of CH in newborns were 76.09%, 71.74% and 0.795. D. The sensitivity, specificity and AUC of combined detection of TSH, FT4 and gestational age for CH in newborns were 95.75%, 95.75% and 0.913.

Table 4. Single factor analysis for CH in newborns

Factor	Study group n = 46	Control group n = 46	t/X ²	P
Gender			0.044	0.835
Male	24 (52.17)	25 (54.35)		
Female	22 (47.83)	21 (45.65)		
Delivery method			0.050	0.822
Natural childbirth	31 (67.39)	32 (69.57)		
Caesarean section	15 (32.61)	14 (30.43)		
Maternal thyroid abnormality			17.51	< 0.001
Yes	31 (67.39)	11 (23.91)		
No	15 (32.61)	35 (76.09)		
Fetal distress			21.70	< 0.001
Yes	30 (65.22)	8 (17.39)		
No	16 (34.78)	38 (82.61)		
Maternal underlying disease				
Hypertension	13 (28.26)	10 (21.74)	0.522	0.470
Diabetes	22 (47.83)	2 (4.35)	22.55	< 0.001
Gestational age (week)	33.61 ± 3.26	36.84 ± 2.55	5.293	< 0.001
Weight (kg)			0.045	0.812
≥ 3.5	27 (58.70)	28 (60.87)		
< 3.5	19 (41.30)	18 (39.13)		

brain and nervous system [10]. Therefore, the early diagnosis of CH in newborns has an important clinical significance for improving CH in newborns [11]. However, the symptoms of hypothyroidism are not obvious in the neonatal stage, so the laboratory indicators of neonates are the main basis for the diagnosis of CH [12].

In our study, the single and combined detections of TSH, FT4 and gestational age were carried out on the diagnosis of CH in newborns. In the detection of TSH and FT4, the venous blood of the neonates was collected 3

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Table 5. Assignment table

Factor	Assignment
Maternal thyroid abnormality	yes = 1, no = 2
Fetal distress	yes = 1, no = 2
Maternal diabetes	Yes = 1, no = 2
Gestational age	≥ 33 weeks = 1, < 33 weeks = 2

days after birth. The reason is that the neonatal bodies need a series of changes and adjustments to adapt to the external environment after birth, including the adjustment of hypothalamus-pituitary-thyroid system [13]. After birth, the surrounding environment is lower than the mother's body. The serum TSH of the neonates will increase temporarily, and the increase of TSH will promote the release of T3 and T4 from the thyroid gland. Conversely, T3 and T4 can regulate the secretion of TSH from the pituitary gland by negative feedback, which makes the physiological TSH peak alleviated 2 days after birth. Therefore, collecting samples 3 days after birth can exclude the effect of physiological TSH peak on the results [14, 15]. Our results suggested that the serum TSH in the study group was higher than that in the control group, and the serum FT4 and gestational age in the study group were lower than those in the control group. It was indicated that the serum TSH, FT4 of neonates with CH were different from those in the normal neonates, which can be used as diagnostic indicators. The diagnostic values of single and combined detections of TSH, FT4 and gestational age for CH in newborns were analyzed and compared. The results indicated that TSH, FT4 and gestational age have certain diagnostic value for CH in newborns. The AUC of TSH was slightly higher than that of FT4 and gestational age for detecting CH in newborns, but the sensitivity and AUC of combined detection of TSH, FT4 and gestational age were higher than those of single detection of TSH, FT4 and AUC for CH in newborns. It was indicated that the combined detection of TSH, FT4 and gestational age had higher diagnostic value for CH in newborns. Some studies [16] revealed that the morbidity of CH screened by serum TSH and FT4 was basically consistent with that reported in many literatures [17, 18]. It was also suggested that TSH and FT4 had higher screening value for CH in newborns, which was consistent with our conclusion.

For the neonates, in addition to timely diagnosis and treatment of CH, the factors affecting the incidence of the disease should be also analyzed to prevent the occurrence of the disease by controlling various etiologic factors [19]. Therefore, the factors affecting CH in newborns were analyzed. The results

showed that there was no remarkable relationship between gender, weight and delivery method of neonates and CH in newborns, but the maternal thyroid abnormality, fetal distress, gestational age, and maternal diabetes were associated with CH in newborns. The factors of CH in newborns were analyzed by logistic regression analysis to further confirm the independent risk factors for CH in newborns. It has been shown that the maternal thyroid abnormality, fetal distress, maternal diabetes, and gestational age < 33 weeks were independent risk factors for CH in newborns. Some studies [19] have reported that if pregnant women with thyroid dysfunction during pregnancy are not detected and treated in time, it is likely to have adverse effects on the fetus, such as CH and mental retardation. Many studies [20, 21] also showed that the abnormal thyroid dysfunction or hypothyroidism of pregnant women during pregnancy will lead to the thyroid dysfunction of neonates. Many studies [22] indicated that regarding gestational age, the probability of thyroid dysfunction in preterm infants was markedly higher than that in term infants. Some studies [23] explained that premature delivery may lead to immature thyroid development in preterm infants, and the incomplete development of hypothalamus-pituitary-thyroid axis is one of the main factors of CH in newborns. The maternal diabetes affects the fetus in many ways, not just the thyroid of the fetus. But the mechanism of maternal diabetes affecting fetal thyroid function is still unclear [24]. In terms of fetal distress, some studies [25] believed that when the fetus suffered from fetal distress, there would be hypoxia. Hypoxia could inhibit the activity of thyroid-5'-deiodinase, which would lead to thyroid dysfunction in the fetus. All the above studies have proved and explained our conclusion well.

In conclusion, TSH, FT4 and gestational age have higher predictive value for CH in newborns, and the combined detection has the highest predictive value, which can be applied

Table 6. Multi-factor analysis for CH in newborns

Factor	W	SE	OR	95% CI	P
Maternal thyroid abnormality	24.387	0.391	7.026	0.338~15.236	< 0.001
Fetal distress	9.234	0.458	4.059	1.541~10.054	0.003
Maternal diabetes	5.029	0.386	2.391	1.113~5.129	0.028
Gestational age	5.473	0.331	2.639	1.044~13.251	0.015

as one of the optimal screening schemes for CH in newborns. And the maternal thyroid abnormality, fetal distress, maternal diabetes and gestational age < 33 weeks are independent risk factors for CH in newborns. The occurrence of CH in newborns can be avoided by preventing these factors. However, there are also some deficiencies in this study. For example, due to the lack of case data and small sample size, there may be some errors in our conclusions. In addition, other thyroid hormone indicators were not included in the diagnostic indicators. Therefore, whether our scheme is optimal still needs further confirmation. In the future, the sample size will be increased and more clinical indicators will be included for further research.

Disclosure of conflict of interest

None.

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