




## Assessment of intelligence quotient score in children at the age of six with suspected congenital hypothyroidism: A retrospective cohort study

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### Abstract

**Background:** The clinical suspicion of Congenital Hypothyroidism (CH) is identified by abnormal results in the first test of Thyroid Stimulating Hormone (TSH) (5-9.9 mIU/L), and normal results in re-test (TSH<4 mIU/L). The CH has a contribution to physical and mental health. This study aimed to determine the Intelligence Quotient (IQ) score in children with suspected congenital hypothyroidism.

**Methods:** This research is a retrospective cohort study conducted in Mashhad, Iran. The IQ scores of 1976 children at the age of 6 were considered as an outcome variable. The history of CH screening for each newborn was assessed, then all suspected CH newborns that diagnosed healthy in re-test were considered as an exposed group, the effects of this situation on IQ score was assessed using logistic regression. All analysis was performed in STATA.

**Results:** The averages of IQ score ( $p<0.001$ ), weight ( $p=0.024$ ), and height ( $p<0.001$ ) in the exposed group were lower than the unexposed group. The exposed group was related to those whose parental education was less or equal to 12 years ( $p<0.001$ ). Similarly, the history of CH and maternal education for  $\leq 12$  years were detected as risk factors for having an IQ score of  $<90$  in children.

**Conclusion:** Aside from the link between parental education and clinical suspicion of CH in neonates, our findings underline the possible strong effect of CH status and maternal education for  $\leq 12$  years on reducing IQ scores in the next years of child life.

**Keywords:** Intelligence quotient, Suspected CH newborn, Congenital hypothyroidism

**Conflicts of Interest:** None declared

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### Introduction

Congenital hypothyroidism (CH) is an important cause of intellectual disability (1-3). Accordingly, there is an

inverse relationship between intelligence quotient (IQ) and CH (4). The incidence of CH is different across the

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#### ↑What is “already known” in this topic:

Suspected newborns to congenital hypothyroidism will be considered as a healthy when their re-test result is normal, and they are omitted from follow up consequently. Clinical suspicion of Congenital Hypothyroidism may be raised due to congenital hypothyroidism or laboratory error. This congenital disease may impose an influence on physical health, mental health, and growth.

#### →What this article adds:

Parental education for  $\leq 12$  years was related to the clinical suspicion of congenital hypothyroidism in newborns. This disease in neonates reduces mean weight and height at the age of 6 years old. Besides, clinical suspicion of CH and maternal education for  $\leq 12$  years cause a low IQ score in children. Therefore, newborns without confirmed CH in re-test may display growth-related disorders within the next years of their life.

world and is higher in Asians compared to American and European populations (5-10). Besides, it shows a difference between various regions in Iranian population (rang 1:400 to 1:1000) (11-15). Main cause of CH is unknown(4). According to guidelines (4, 16), newborns with the level of thyroid-stimulating hormone (TSH)  $>10$  mu/l are considered as CH cases and they need to be under treatment with levothyroxine. However, TSH between 5 to 9.9 is classified as suspected CH (17, 18), and a second specimen two weeks after birth is needed to be obtained (19). If the re-test result is normal (TSH $<5$  mu/l), there is no need for intervention, and newborns will be omitted from the follow up (11, 20). The Incidence of suspected CH in Iran is 3.46%, most of which, are not confirmed in the re-test (21). The lack of confirmed CH cases may be related to minor disorders which result in a malfunction in congenital thyroid or can be caused by an error. However, there is still inadequate evidence for defining this status (19). Only a few retrospective studies suggest a decrease in IQ score a related factor for subclinical CH (20, 22). Besides, children with a history of subclinical CH are at risk of behavioral problems and possible impaired growth(22), and this raises the possibility that children without a history of confirmed SCH may be exposed to similar risks (20, 23), although the over and under-treatment with levothyroxine itself can be considered a risk factor in CH children (24). This study aimed to determine the role of IQ score at the age of 6 in suspected newborns to congenital hypothyroid.

## Methods

This was a retrospective cohort study conducted in Mashhad in 2018. In this study, we used data from a Pre-school test, Intelligence Quotient (IQ) score, weight (kg) and height (cm) for all children at age 6. We used information of 1973 children whose parents announced their consent for participation in this study.

Demographic variables and health information such as the result of CH screening (history of Thyroid function in the first days of birth), mode of delivery; parent's age, and socioeconomic status (parent's education and job, family size) were extracted from health care cards for each child. Three children excluded from the analysis due to the lack of records for CH screening results.

The Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition (WPPSI-IV) is the latest edition of the individually administered early childhood intelligence test. The full-scale IQ score is determined by a formula that adds both verbal and performance IQ scores. The Persian version of this tool shows high validity (0.91) and reliability (0.76) (25). The full-scale IQ (FSIQ) which can be calculated by this tool, ranges from 45–155. ( a score beyond 130 is considered superior or "gifted", 120-129 is "very high", 110-119 are considered "bright normal", and anything less than 90 is considered low average) (26).

Based on the usual approach for CH screening in Iran, a few drops of blood is taken from the heel of the neonates, and then poured on a filter paper for analysis and measurement by using the enzyme-linked immune sorbent assay (ELISA) technique. According to the national protocol

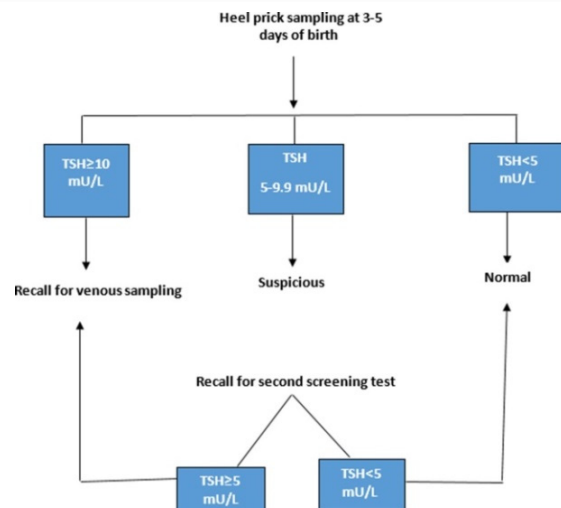


Fig. 1. The protocol of screening CH in Iran

in Iran, a TSH level of  $< 5$  m U/L for neonates age 3-7 days is considered as normal. Other results are categorized as suspicious ( $5 < \text{TSH} < 9.9$ ) and whose recall for venous sampling ( $\text{TSH} > 10$ ). Re-test is recommended for suspicious cases to be done (TSH range: 5- 9.9 m U/L). If the re-test shows a TSH  $< 5$ , it is usually considered as a normal (healthy newborn), and this neonates omitted of the follow up (Fig. 1).

In this study, the children who were suspected for congenital hypothyroidism ( $\text{TSH} = 5-9.9$ ) in the first test, and normal in the re-test ( $\text{TSH} < 5$ ) were considered as an exposed group, while the non-exposed group had normal result in the first test ( $\text{TSH} < 5$ ). The mean-2SD was considered as a cut point to determine normal or abnormal IQ scores in two groups. Baseline variables were parent's education ( $\leq 12$  years or  $> 12$  years), parent's job (unemployed or others), family size ( $\geq 4$  or  $< 3$ ), mode of delivery (vaginal delivery or cesarean section), and gender.

The proposal related to this study was approved by the ethical committee of Mashhad University of Medical Sciences (#89102). The authors reported the overall results of the study.

## Statistical Analysis

For data analysis, STATA statistical package, version 12 (STATA Corporation, College Station, TX, USA, 2009) was used. Firstly, we described data by frequency, percentage, mean, and standard deviation; second, we used t-TEST, Chi-square, or Fisher exact test to examine the associations of baseline categorical variables with outcomes. In the following, the risk factors for abnormal IQ were evaluated by the logistic regression model, covariates in crud analysis ( $p < 0.2$ ) were assessed by adjusted logistic regression for control of potential confounders. The Odds ratio estimated, and P-value 0.05 was considered statically significant for all tests.

## Results

In a total of 1973 children, the distribution of gender was approximately equal, including girls ( $n=996$ , 50.43%)

and boys (n=977, 49.57%). The incidence of suspected congenital hypothyroidism ( $5 < \text{TSH} < 9.9$ ) was 3.18% (CI95% 2.49, 4.06). However, all tests were in the normal range after the re-test ( $\text{TSH} < 4$ ). Accordingly, 70% of newborns were screened at the age of 3-5 days after birth, 10.6% at 6-40 days, 0.6% at  $>40$  days, and 18.7% of newborns were tested in less than 72 hours after birth.

The history of cesarean section delivery was detected in 52% and the mean of height was  $117.76 \pm 5.82$  (range: 90-155). Similarly, the mean weight was  $20.47 \pm 3.99$  (range: 10-45), and the average IQ score was  $98.49 \pm 4.77$  (range: 74-152). The IQ score was 98.18 (range: 97.89-98.48) and 98.79 (range: 98.49-99.09) in boys and girls, respectively. We considered a cut point of 89.99 to determine the normal IQ score in this data. IQ of  $< 90$  was found in 99 (5.03%) and IQ of  $\geq 90$  in 1871 (94.97%) participants.

### Characteristics of exposed and unexposed groups

From a total of 1970 children with a history of CH screening result, 1906 had  $\text{TSH} < 5$  (unexposed group) and

64 children had  $\text{TSH} 5-9.9$  in the first test, and all was healthy in the re-test (exposed group). The baseline variables according to the exposed and unexposed group summarized in Table 1. The result indicated that there is a significant relationship between the level of parental education and level of  $\text{TSH}$  in newborns ( $p < 0.001$ ), however, there is no relationship between parent's age and delivery mode with  $\text{TSH}$  level ( $p > 0.05$ ). In this cohort study, not only the average IQ score in the unexposed group was higher than the exposed group ( $p < 0.001$ ), but also the mean difference of weight and height in the unexposed and exposed group was statistically significant ( $p < 0.050$ ). An unexposed group was heavier ( $p = 0.028$ ) and taller ( $p < 0.001$ ) than the exposed group (Table 1).

Factors associated with abnormal IQ in children at age of 6 is presented in Table 2. The following factors were included in the logistic regression model: Parent's education ( $\leq 12$  years or  $> 12$  years), parent's job (unemployed or others), delivery mode (normal vaginal delivery or cesarean section), sex and  $\text{TSH}_1$  ( $\text{TSH} \geq 5$  or  $\text{TSH} < 4.99$ ).

Table 1. Comparison of baseline characteristics in the exposed and unexposed group

Variable	Exposed group n=64	Unexposed group n=1906	Total	p
Sex (n%)				
Male	32 (3.28%)	943 (96.72%)	975	0.944
Female	32 (3.23%)	960 (96.77%)	992	
Delivery mode (n%)				
Cesarean	34 (3.36%)	979 (96.64%)	1013	0.865
Vagina	30 (3.22%)	902 (96.78%)	932	
Mother's education				
$\leq 12$ years	46 (5.16%)	846 (94.84%)	892	$< 0.001$
$> 12$ years	16 (1.53%)	1033 (98.47%)	1049	
Father's education				
$\leq 12$ years	52 (5.26%)	936 (94.75%)	988	$< 0.001$
$> 12$ years	12 (1.25%)	947 (98.75%)	959	
Mother's job				
Housewife	60 (3.54%)	1633 (96.46%)	1693	0.082
Others	3 (1.34%)	221 (98.66%)	224	
Father's job				
Unemployed	1 (2.78%)	35 (97.22%)	36	0.860
Others	63 (3.31%)	1842 (96.69%)	1905	
Family size (mean $\pm$ SD)	4.31 $\pm$ 1.46	4.05 $\pm$ 1.08		0.064
Mother's age (mean $\pm$ SD)	32.68 $\pm$ 5.75	32.82 $\pm$ 5.38		0.845
Father's age (mean $\pm$ SD)	36.49 $\pm$ 6.66	37.14 $\pm$ 6.24		0.425
IQ score (mean $\pm$ SD)	86.01 $\pm$ 0.548	98.91 $\pm$ 0.095		$< 0.001$
Weight (kg) (mean $\pm$ SD)	19.35 $\pm$ 0.56	20.51 $\pm$ 0.09		0.028
Height (cm) (mean $\pm$ SD)	114 $\pm$ 0.87	117 $\pm$ 0.13		$< 0.001$

Table 2. Factors associated with abnormal IQ in children at age 6 years old

variable	Unadjusted			Adjusted*		
	OR	p	CI 95%	OR	p	CI 95%
Mother's education	$> 12$ years	1	-	-	1	-
	$\leq 12$ years	2.96	$< 0.001$	(1.47, 3.55)	2.30	0.014
Father's education	$> 12$ years	1	-	-	1	-
	$\leq 12$ years	2.28	$< 0.001$	(1.47, 3.55)	0.81	0.54
Mother's job	Others	1	-	-	1	-
	Housewife	3.12	0.027	(1.13, 8.58)	2.04	0.25
Father's job	Others	1	-	-	-	-
	Unemployed	1.12	0.877	(0.26, 5.73)	-	-
Mother's age	$\leq 35$	1	-	-	-	-
	$> 35$	1.27	0.27	(0.82, 1.98)	-	-
Gender	girl	1	-	-	1	-
	boy	1.34	0.154	(0.89, 2.02)	1.63	0.08
$\text{TSH}_1$	$\text{TSH} < 4.99$	1	-	-	1	-
	$\text{TSH} \geq 5$	151.85	$< 0.001$	(77.47, 297.6)	139.74	$< 0.001$
Delivery type	Vaginal	1	-	-	-	-
	Caesarean	1.04	0.834	(0.69, 1.57)	-	-

\* Prob  $> \chi^2 = 0.0000$ , Log likelihood = -228.9236, Pseudo R2 = 0.3713

After adjusting for other factors, TSH1 and Mother's education level were significantly associated with abnormal IQ ( $p < 0.001$ ,  $p = 0.014$ ). On the other hand, odds of abnormal IQ were 139.74 times more likely in children with a history of TSH1  $> 5$  compared to children with a history of normal neonatal TSH1 ( $p < 0.001$ ). Besides, odds of abnormal IQ were 2.30 times more likely in mothers who have education  $\leq 12$  years compared to  $> 12$  years ( $p = 0.014$ ). Other independent variables were not significantly correlated with abnormal IQ.

### Discussion

We demonstrated an association between abnormal neonatal TSH and IQ score in the next years of life in children who were suspicious of congenital hypothyroid (TSH=5-9.9) in the first test and diagnosed healthy (TSH $< 4$ ) in re-test.

Our findings indicated that children with a history of abnormal neonatal TSH have a lower average of weight and height at the age of 6 compared to the other children with normal history, besides, they have a greater risk for IQ score of less than 90, and these findings are in line with Calaciura and colleagues findings (27, 28). Thyroid hormone is essential for normal growth of fetus and infant (29). Therefore TSH disorder during early life may be related to the development of several central transmitter systems that leads to immutable morphological and biochemical abnormalities (28). Neonatal with low thyroid hormone levels (even only for few days) are at the high risk of the impaired developmental outcome, impairment of mental and physical growth (30, 31), and abnormal thyroid function (13, 32-34).

The results also showed that maternal education could have an impact on IQ score in children, as mothers with lower education had a greater risk of having a child with abnormal IQ score (IQ $< 90$ ) at the age of 6-7. Obtained data is similar to the findings from the ELGAN cohort study. According to this study, children belongs to women with  $\leq 12$  years of education have a high risk of a low IQ score at the age of 10 (2). Thus, available data are in line with other studies that have evidence of the relationship between parent's education and IQ scores in children (2, 35, 36).

Despite the previous studies which demonstrated that only father's education status affects TSH in newborns (37), evidence of our study suggests that parent's education status was related to TSH level in newborns, and mothers with lower education had more probability of having newborn with TSH  $> 5$  mIU /L. In a study conducted in Tianjin-China, low maternal education was considered as a predictor of CH (38), and over time, mothers with higher educational status had a lower risk of bad perinatal outcomes (39). Furthermore, mothers who have a higher level of education may be more willing to utilize prenatal care services (40, 41), and are more prone to avoid harmful behaviors (42). Besides, they have better nutrition behaviors for themselves and their children (43). Most studies pay less attention to the role of maternal education as a risk factor than biological factors that can influence neonatal thyroid function (44, 45).

According to our findings, the incidence of clinical suspicion of CH was 3.18%, while all cases were healthy in the re-test (100% healthy). This is similar to the findings of a previous survey in Iran (21). Although there is controversy about unequal (10) or equal sex ratio (girl/boy) of CH (46), our results indicate an equal sex ratio for clinical suspicion of CH (girl: boy 1:1). On the other hand, the risk of clinical suspicion of CH is equal in both sexes of neonates (47). Despite some reports indicating for the association between Cesarean delivery and abnormal TSH in the newborn (37, 48, 49), such relation was not confirmed in our study (10, 46, 50).

### Study limitations

The retrospective nature of data was a limitation in this study, for example, lack of information about family income and lifestyle for each child 6 years ago which may influence IQ score.

### Conclusion

Aside from the association between parental education for  $\leq 12$  years and clinical suspicion of CH status in neonatal, our findings underline the possible effect of clinical suspicion of CH status and maternal education for  $\leq 12$  years on a reduced IQ score in the next years of child life.

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### Conflict of Interests

The authors declare that they have no competing interests.

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