

## Intelligence Quotient at the Age of Six years of Iranian Children with Congenital Hypothyroidism

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Received: July 27, 2016; Initial Review: November 05, 2016; Accepted: September 01, 2017.

**Objective:** To evaluate the success rate of the National newborn screening program in maintenance of intelligent quotient (IQ) of children with congenital hypothyroidism in Iran.

**Design:** Retrospective cohort study.

**Methods:** The IQ scores, in three subsets of verbal, non verbal (Performance) and full scale IQ, of 240 children diagnosed with Transient congenital hypothyroidism (TCH) and Permanent congenital hypothyroidism (PCH), from 5 provinces in 5 different geographical areas of Iran, were measured at the age of 6 years using revised Wechsler pre school and primary scale of intelligence and compared with 240 healthy children. We used independent sample t test and two-way ANOVA for data analysis.

**Results:** Mean of verbal, performance, and full scale IQ scores were lower in the CH cases (permanent and transient) than the control group. Most of the IQ differences in two studied groups related to the PCH cases ( $P=0.005$ ). Mean difference of IQs between children in the two groups in Yazd province (center of Iran) was higher than other provinces, and they also had significantly lower IQ than their control (healthy) children ( $P=0.001$ ). No treated child had  $IQ<70$ .

**Conclusion:** Although mean IQs of CH children was lower than their controls, IQ of all treated CH cases were close to the healthy children.

**Keywords:** Management, Neonatal screening, Outcome.

Published online: September 26, 2017. PII:S097475591600092

Congenital hypothyroidism (CH) is considered as one of the most important preventable causes of mental retardation in children [1]. The incidence of CH is different among neonates of various countries of the world and ranges from 1:2000 to 1:4000 [2-6], the incidence of CH in different areas of Iran is reported to vary from 1:400 to 1:1000 [7,8].

In Iran, a National program of neonate screening was established from 2004-2005 [9]. In this program, thyroid-stimulating hormone (TSH) is measured as a primary test, and positive tests are confirmed by serum thyroxine (T4). By the end of 2015, over 9 million neonates were screened and over 10 thousand children were diagnosed with CH and treated with levothyroxine (L-Thyroxine).

The evaluation of this mass screening program, particularly from the view of maintaining the IQ of children with CH at the national level has been done [10,11], but there have been no systematic long-term follow-up studies for evaluation of intervention/treatment outcomes among hypothyroid children diagnosed by the nationwide newborn screening program in Iran. This study was done to assess the IQ of hypothyroid children

diagnosed by national program of CH screening at age of 6 years, compared with healthy children in Iran.

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### METHODS

This was a retrospective cohort study conducted in five provinces in different geographical areas of Iran. A total of 480 children in two study groups, including 240 children with CH and 240 healthy children were investigated in this comparative study. We first specified our samples based on mean difference sample size formula, then we modified our selected samples based on the number of children diagnosed with CH in all five studied provinces.

After calculation of primary sample size ( $N=314$  children), we modified it based on all diagnosed hypothyroid children in a year ( $N=1000$  children) and final sample size in each group was obtained as 240.

Children with CH were cases diagnosed by National newborn screening program and treated with levothyroxine, six years before this study. These cases were selected by systematic random sampling from National newborn screening program registry in Iran. For

each case, we took one healthy child as the control and matched it with CH child based on age, sex and place of birth. For age-matching, we selected a child that was born at  $\pm 3$  month intervals of CH cases. The ethical approval of this research was given by Shahid Beheshti University of Medical Sciences ethics committee.

Iran has 31 provinces; all 31 provinces of the country were divided into 5 regions, viz. North (including 7 provinces), South (including 5 provinces), East (including 5 provinces), West (including 8 provinces) and Center (including 6 provinces); then we randomly selected one province in each region consisting of Mazandaran, Khuzestan, Razavi Khorasan, Kurdistan and Yazd, respectively. The number of samples in each province was determined based on the number of children diagnosed with CH or by probability proportional to size (PPS) sampling method. Sampling in each of five selected provinces was conducted by systematic sampling method using the list of identified hypothyroid children. The intelligence quotient (IQ) scores, were measured at age six years using revised Wechsler Pre school and Primary Scale of Intelligence (WPPSI-R) and compared with the control group.

All analyses were conducted using STATA version 14 using independent-sample t-test and two-way ANOVA. We also checked two main assumptions of independent-samples t-test and ANOVA including normality of IQ as dependent variable and homogeneity of variances by Kolmogorov–Smirnov test and Levene’s test, respectively.

**RESULTS**

A total of 240 CH cases and 240 healthy (control) children were enrolled (49.2% males). One hundred thirty one (54.6%) of CH cases had transient congenital hypothyroidism (TCH) and 109 cases (45.4%) had permanent congenital hypothyroidism (PCH). Demographic characteristics of studied children are presented in **Table I**. The number of children enrolled in each of the CH and control group from the five sites was 69 (Khuzestan), 51 (Razavi khorasan), 50 (Kurdistan), 40 (Yazd), and 30 (Mazandaram).

Mean (SD) of IQ for CH cases and healthy children were 101.1 (13.7) and 104.5 (14.5), respectively ( $P=0.01$ ). This difference was also seen in two main components of IQ (verbal and non-verbal IQ).

**Table II** shows the relationship between mean IQ and other categorical variables (province of residence, sex, and type of hypothyroidism) in two study groups. The mean difference for verbal, non-verbal and full-scale IQs between CH and control children were 3.2, 3.1 and 3.4, respectively. There were significant differences between province of residence and the mean IQ of children in both two groups ( $P<0.05$ ). The results of HSD test for mean verbal IQ showed that there are statistical significant differences between Kurdistan and Yazd ( $P<0.001$ ), Yazd and Khuzestan ( $P<0.001$ ), Razavi Khorasan and Khuzestan ( $P<0.001$ ) in control groups and also there were statistical significant differences between Kurdistan and Yazd ( $P=0.002$ ), Yazd and Khuzestan ( $P<0.001$ ), Razavi Khorasan and Khuzestan ( $P=0.01$ ) in CH cases. The results of HSD test for mean non-verbal IQ was only statistical significant between Khuzestan and Mazandaran provinces ( $P=0.01$ ). Although HSD test results for mean difference of Full scale IQ showed significant difference between Kurdistan and Yazd ( $P=0.02$ ), Yazd and Khuzestan ( $P<0.001$ ), Razavi Khorasan and Khuzestan ( $P=0.02$ ), Khuzestan and Mazandran ( $P<0.001$ ) in control groups but the mean difference of Full scale IQ was only significant between Khuzestan and Mazandran in CH cases ( $P=0.04$ ).

There were no statistical significant differences between IQ and type of CH. There were statistically significant differences in mean of full scale IQ between PCH cases and their controls ( $P=0.005$ ), and also for verbal IQ ( $P=0.01$ ) and non-verbal (Performance) IQ ( $P=0.02$ ).

**DISCUSSION**

In this study, we evaluated the success rate of early detection and timely T4 supplementation in children with CH via measuring the IQ of treated cases at age of 6 years and comparing with healthy children as their control group. Our results demonstrated that the mean (SD) IQ of

**TABLE I** DEMOGRAPHIC CHARACTERISTICS OF THE STUDY PARTICIPANTS ( $n=480$ )

Characteristic	CH cases ( $n=240$ ),	Control group ( $n=240$ )	Total
Gestational age, no. (%)			
Preterm (<37 weeks)	24 (10)	17 (7.1)	41 (8.5)
Full term (37-42 weeks)	209 (87.1)	219 (91.2)	428 (89.2)
Age (y), mean (SD)	6 (0.4)	6 (0.3)	6 (0.35)
Weight (g) at birth, mean (SD)	3198.5 (605.1)	3294.1 (553.2)	3246.34 (569.4)

**TABLE II** RESULTS OF IQ ASSESSMENT IN THE STUDY POPULATION (N=480)

	Verbal IQ		Non verbal IQ		Full scale IQ	
	CH cases	Controls (Performance) IQ	CH cases	Controls	CH cases	Controls
<i>Province</i>						
Khuzestan	94.7 (17.6)	96.5 (16.6)	99.5 (16.1)	100.3 (15.7)	97.4 (15.7)	98.5 (16.4)
Razavi Khorasan	103.3 (13.9)*	109.2 (13.6)*	99.7 (13.1)	101.9 (14.1)	101.5 (12.3)	106.1 (12.9)
Kurdistan	98.4 (12.4)	99.5 (14.4)	103.9 (13.2)	104.9 (10.9)	101.3 (12.4)	102.3 (11.7)
Yazd	110.4 (11.8)#	116.9 (10.6)#	95.5 (11.3)	103.8 (9.3)	‡103.4 (10.9)	‡111.2 (9.4)
Mazandaran	103.2 (17.3)	104.3 (18.2)	103.8 (18.2)	110.4 (20.6)	105.7 (15.2)	110.1 (16.3)
Total	101.0 (15.8)	104.2 (16.5)	100.3 (14.7)	103.4 (14.5)	101.1 # (13.7)	104.5 # (14.5)
<i>Type of CH</i>						
TCH	100.6 (15.9)	101.9 (16.0)	101.1 (14.7)	102.8 (13.7)	101.1 (13.9)	102.6 (13.9)
PCH	101.6 (15.6)#	107.0 (16.8)#	99.4 (14.6)	104.1 (15.5)	^101.2 (13.6)	^106.7 (14.9)
<i>Gender</i>						
Boys	102.8 (14.9)	105.8 (15.7)	102.4 (14.1)	103.9 (13.3)	102.9 (13.3)	105.6 (13.9)
Girls	99.3 (16.5)	102.7 (17.2)	#98.3 (14.9)	#102.9 (15.7)	*99.3 (13.9)	*103.4 (15.1)

\*P=0.03; #P=0.01; \$P<0.001; ‡P=0.001; ^P=0.005. TCH: Transient Congenital Hypothyroidism; PCH: Permanent Congenital Hypothyroidism; TSH level >10 mU/L, 1-3 months after discontinuation of levothyroxine therapy in children older than 3 year).

CH cases [101.1 (13.7)] after adjustment for age, sex and socioeconomic status (SES) was significantly lower than their controls [104.5 (14.5)]. Although, the results indicated lower mean IQ scores of CH cases comparing their controls, the success rate of CH detection and treatment at first weeks after birth is evaluated high because mean IQs of all cases at age 6 years were within the normal range.

In this study, we showed that there are no significant differences between CH patients and their controls in 6 years after treatment. Our results are consistent with many previous studies [12,13]. Previous studies indicate that severity of CH (defined by initial thyroxine at the moment of diagnosis and by skeletal maturation) is most important individual risk factor for neuropsychologic development in patients with CH [14]. In this study, we showed that the type of hypothyroidism (transient or permanent) is a main risk factor in IQ deficit, and despite timely detection and treatment of CH cases in our program, there are more IQ deficit in children with permanent rather than transient CH. The difference between the IQs of cases and controls in PCH was 4 times more than TCH cases. In a previous study, it was demonstrated that there is no associations between Transient hypo-thyroxinemia of prematurity (THoP) and neuro-developmental outcome at age 19 years [15]. Our results are also consistent with the study of cognitive and motor outcome of early treatment of 82 Dutch CH patients [16], where patients with severe CH had lower verbal,

performance, and full-scale IQs than the normative population, whereas IQ scores of patients with moderate and mild CH were comparable to those of the normative population [16].

In addition to the genetic factors, age, sex and SES are considered most important confounders when we compare the difference between the IQ of CH cases and healthy children [17-19]. In this study, we approximately eliminate the effect of these potential confounders with individually matching of CH subjects and their controls based on age, sex and SES during the primary sampling process. We used valid and widely accepted IQ test. Comparing the IQs of patients with CH in two separate CH types (TCH and PCH) and subjects sampling from different areas of the country were another strengths of current study.

Although our findings highlight the success of Iran National program of neonatal screening for detection and treatment of CH cases, the IQ of hypothyroid children was lower than healthy children and more emphasis should be placed on the strengthening the surveillance system, particularly timely visit by physician and systematic controlling of serum thyroid hormones level to assure thyroxine compensation in children with CH. We strongly suggest systematic surveillance of children with CH during first 6 years of life, particularly in PCH cases which may ensure better control of congenital hypothyroidism, and prevent its adverse effects.

**WHAT IS ALREADY KNOWN?**

- Children with congenital hypothyroidism have improvement in IQ after timely detection and treatment.

**WHAT THIS STUDY ADDS?**

- Neonates identified with congenital hypothyroidism at birth by neonatal screening had mean IQ lower than unaffected children at 6 years of age but none had a sub-normal (<70) IQ.

*Acknowledgements:* This work was supported by Department of Endocrinology and Metabolism, Ministry of Health, Tehran, Iran in collaboration with Department of Epidemiology at Shahid Beheshti University of Medical Sciences.

*Contributors:* HS, SY, KR, NA: study concept and design. KR, YM: analysis and interpretation of data and drafting the manuscript. KE, AK: drafting the manuscript. All authors approved the final manuscript.

*Funding:* Department of Endocrinology and Metabolism, Ministry of Health, Tehran, Islamic Republic of Iran.

*Competing interests:* None stated.

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