

Intelligence quotient in children with congenital hypothyroidism: The effect of diagnostic and treatment variables

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Background: Considering the high prevalence of congenital hypothyroidism (CH) in Isfahan, the intelligence quotient (IQ) of children with CH and the effect of diagnostic and treatment variables on it were investigated during the CH screening program. **Materials and Methods:** A total of 120 children in three studied groups were studied in this comparative study the IQ score, in three subsets of verbal IQ, performance IQ and full scale IQ, of children diagnosed with transient congenital hypothyroidism (TCH) and permanent congenital hypothyroidism (PCH) was measured using revised Wechsler pre-school and primary scale of intelligence and compared with the control group. The relation between IQ score with time of treatment initiation and screening thyroid stimulating hormone (TSH) level was evaluated in all studied groups. **Results:** Mean of verbal IQ, performance IQ, and full scale IQ score was significantly higher in the control group than CH patients (both permanent and transient) In PCH patients though it was not significant, there was a negative relationship between verbal IQ, performance IQ and full scale IQ and screening TSH and age of treatment initiation. In TCH patients, there was negative and significant relationship between verbal IQ ($r = -0.40$) and full scale IQ ($r = -0.38$) and age of treatment initiation ($r = -0.46$). **Conclusion:** Mean IQ score in both PCH and TCH patients were lower than the control group, which correlates negatively with treatment initiation time. Though CH screening and early treatment has improved the prognosis of patients, but early and high dose of treatment in children with CH is recommended.

Key words: Congenital hypothyroidism, intelligence quotient, permanent, transient, Wechsler pre-school and primary scale

INTRODUCTION

Thyroid hormones are critical for central nervous system (CNS) maturation specially from the early stage of fetal life to 2-3 years of age.^[1] This fact has led to the development of neonatal screening of congenital hypothyroidism (CH), which initiated from 1975 and improved during the time, in a way that most countries perform CH screening world-wide. This advance results in significant improvement in eradication of abnormal neurodevelopmental outcome of the disease.^[2]

CH consider the common cause of treatable mental retardation with prevalence of 1/3,000-4,000 live birth. Proper management of the disease is crucial for achieve favorable results in this field, which contains early diagnosis, prompt treatment, and regular follow-up during the 1st year of life.^[3]

Several studies investigated many related factors to the management of the disease and their impact on its outcome specially mental development including; severity of CH (low initial serum thyroxine concentration, delayed skeletal maturation at birth), l-thyroxine

treatment variables (time of treatment initiation and its dosage), level of thyroid stimulating hormone (TSH) during the treatment and follow-up period and different finding obtained in this field. Some of them believed that high dose of levothyroxine treatment has an important effect on the long-term intellectual development of affected infants, whereas others emphasize on the early treatment of the disease.^[4-6]

Some reported that appropriate treatment result in normal development of patients with CH, but others indicated some evidence of intellectual impairment despite early treatment.^[7-10] The most common factor that evaluated for the patients neurodevelopmental outcome is full scale intelligence quotient (IQ). Mean IQ score of CH patients before establishment of CH screening have reported to be 76, whereas after that it increased to 104 comparing with control normal children with mean IQ score of 106.^[11]

CH screening program in Isfahan has been performed since 2002 and the findings showed high prevalence of disease in this region, likewise other parts of Iran. Many researches have been assessed in this field to

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determine the etiology, genetic origin, and risk factors of the disease.^[12-14] The outcome of the screening program was evaluated also,^[15] but the relation between treatment variables and mental development among affected patients has not studied yet. However considering the high prevalence of CH in Iran and Isfahan, mentioned investigation would improve the CH screening program and neurodevelopmental outcome of patients and consequently community health.

MATERIALS AND METHODS

In this comparative study, neonates referred to Isfahan Endocrine and Metabolism Research Center (EMRC) for CH screening in Isfahan enrolled.

CH screening program initiated from 2002 and is continued until now, according to the screening protocol, neonates referred at 3-7 days of birth and TSH is measured by filter paper by heel-prick method. Newborns with abnormal screening results were re-examined and those with abnormal T4 and TSH level on their second measurement (TSH > 10 and T4 <6.5) were diagnosed as CH patient and received treatment and regular follow-up. Hypothyroid neonates underwent treatment at a dose of 10 µg/kg/day as soon as the diagnosis was confirmed, with the monitoring of TSH and T4 during follow-up.

Permanent congenital hypothyroidism (PCH) and transient congenital hypothyroidism (TCH) cases of CH were determined at 3 years old by measuring TSH and T4 concentration 4 weeks after withdrawal of L-T4 therapy. Patients with elevated TSH levels (TSH > 10 mIU/l) and decreased T4 levels ($T_4 < 6.5 \mu\text{g/dl}$) at this time were considered as PCH.^[16]

Neonates participated in CH screening classified in three groups as follows; PCH, TCH, neonates with normal screening results. Neonates with normal screening results classified as the control group. The information of all screening neonates are available and recorded as well as those with TCH or PCH. Hence, age and sex matched children from those with normal screening results were selected and recalled for participating in the study. Studied population in mentioned groups were age and sex matched 4-6 years old children.

The protocol was approved by the Institutional Review Board and Medical Ethics Committee of Isfahan University of Medical Sciences. Written consent was obtained from the parents of CH patients.

The characteristics of all studied children were recorded from their screening profile available at CH screening

center in EMRC. Assessment of IQ in studied children was performed using Wechsler pre-school and primary scale of intelligence.^[17] Children with history of meningitis, fever and compulsion, brain trauma, disabled children, children born after complicated pregnancies and also other non-natives of Iran were excluded from the study.

We used standardized Wechsler scale for use in Iran with acceptable validity and reliability, which included 11 subscales.^[18] Mentioned subscales are classified in two verbal (information, vocabulary, similarities, comprehension, and arithmetic), and performance (animal house, picture completion, mazes, geometric design, and block design) and subtests. Based on the scores of mentioned subtests the verbal IQ, performance IQ and full scale IQ (based on 10 tests included in the verbal and performance is calculated.^[18]

Obtained data regarding demographic characteristics and IQ scale in three studied groups compared using *t*-test in SPSS (PASW) and analysis of covariance tests.

RESULTS

In this study, 120 children studied in three groups as follows; PCH patients, TCH patients, and control group.

The characteristics of studied population are presented in Table 1.

Mean \pm SD of verbal IQ, performance IQ and full scale IQ in studied groups are presented in Table 2.

Covariate test indicated that in PCH patients, though it was not significant, but there was a negative relationship between verbal IQ, performance IQ and full scale IQ and screening TSH and age of treatment initiation. In TCH patients, there was negative and significant relationship between verbal IQ ($P = 0.03$, $r = -0.40$) and full scale IQ ($P = 0.04$, $r = -0.38$) and age of treatment initiation ($P = 0.03$, $r = -0.46$).

Table 1: The characteristics of patients with permanent and transient CH and control group

	Permanent CH patients	Transient CH patients	Control group	P value
Female/male	12/18	9/21	32/28	>0.05
Mean age (year)	4.38 \pm 0.47	4.28 \pm 0.50	4.83 \pm 0.79	>0.05
Mean of screening TSH (mIU/L)	24.9 \pm 19.7	53.8 \pm 43.1	8.9 \pm 1.8	* $P=0.02$ ** $P<0.001$
Mean age of treatment initiation (days)	16 \pm 13.2	18.5 \pm 13.5	-	>0.05

* P value between permanent and transient CH, ** P value between permanent CH and control group and transient CH and control group, CH=Congenital hypothyroidism; IQ=Intelligence quotient; TSH=Thyroid stimulating hormone

Table 2: Mean±SD of verbal IQ, performance (non-verbal) IQ and full scale IQ in patients with permanent and transient CH and control group

Groups/IQ	Verbal IQ	Performance (non-verbal) IQ	Full scale IQ
Permanent CH patients	89.5±17.9	95.9±16.1	92.4±16.3
Transient CH patients	90.5±13.7	97.9±18.3	93.0±15.8
Control group	97.8±14.2	113.3±14.6	105.9±12.9
<i>P</i> value	* <i>P</i> =0.001	* <i>P</i> =0.001	* <i>P</i> =0.002
	** <i>P</i> =0.002	* <i>P</i> =0.002	* <i>P</i> =0/004

P*<0.01 between permanent CH and controls, *P*<0.01 between transient CH and controls, CH=Congenital hypothyroidism; IQ=Intelligence quotient

DISCUSSION

The aim of CH screening programs is to prevent the related mental retardation. Though many studies indicated that these programs are success full in achieving this goal, but others indicated that it depends on many factors and some others indicated that even with appropriate treatment the patients had defect due to the thyroid hormone deficiency during the fatal and early neonatal period.

Considering these facts and the high rate of CH in our community we investigated the relation between diagnostic and treatment variables with intellectual outcome of patients with CH. The results indicated that the mean score of IQ in patients with CH, both transient and permanent forms, was lower than normal children. It was correlate negatively with screening TSH level and timing of treatment in permanent group and with timing of treatment in transient group.

Several studies determined the effect of mentioned factors on IQ of patients with CH and different results have been reported in this field.^[7-10] In current study, though according to our screening protocol the dose of levothyroxine in treatment initiation was 10 µg/kg/day and the mean age of treatment initiation in patients with PCH and TCH was lower than 20 days, the mean IQ level was lower in patients than the control group.

In accordance to our study, Dimitropoulos *et al.* in Switzerland determined the long-term intellectual outcome of patients with CH who was treated at a median age of 9 days and levothyroxine dose of 14.7 µg/kg/d and showed that mean IQ score was significantly lower in CH patients than the control group in spite of earlier treatment with higher dose of levothyroxine.^[9]

In the study of Oerbeck *et al.* in Norway, influence of disease severity and levothyroxine treatment on intellectual outcomes in young adults was investigated. IQ score was measured by Wechsler abbreviated scale of intelligence, according to their results mean of total, verbal, and performance IQ all were lower in patients with

CH comparing with their normal siblings. Mean age of treatment initiation and dose of levothyroxine in studied CH patients was 24.4 days and 8.4 µg/kg/d respectively.^[19]

On the other hand, other studies reported normal IQ score in patients with CH. Kik and Noczyńska studied the general IQ on verbal and non-verbal scale using Wechsler scale among 44 children aged 3.5-18 years detected in screening. Their overall findings were that mental development of the studied children with CH was within normal range and the level of TSH in the screening test and time of treatment initiation had no effect on the mental development of children with CH.^[7]

Arenz *et al.* in Switzerland investigated the intellectual outcome and motor skills in 18 Children with PCH with a median age of 5.5 years using Kaufman assessment battery for children and Motoriktest für vier-bis sechsjährige Kinder.^[4-6] They showed normal intellectual development in their studied patients. Mean IQ score was reported to be 100.4 ± 10.1. Mean of treatment initiation time was 7.2 days with a median levothyroxine dose of 12.0 µg/kg/d. There was a negative significant correlation between screening TSH level and studied variables.^[8]

In this study, the IQ score was not different in PCH and TCH patients and it confirms the fact that all type of CH patients' needs proper treatment during the first year of life for obtaining enough IQ score and mental development. However, it was better to determine the IQ score among different etiologies of PCH for more conclusive results.

Similarly, Calaciura *et al.* in Italy have investigated the intellectual development of children with TCH and indicated that performance IQs using Wechsler scale were systematically lower in the TCH than in the control group. They concluded that the findings strongly suggest that abnormalities in thyroid function at birth, even when transient, can adversely affect long-term intellectual development.^[20]

In both patients with PCH and TCH, there was negative correlation between IQ score and age of treatment initiation. There were controversial results in this field; some were in line with our results, whereas others did not indicate the mentioned association.

In a study in France, the effect of timing of treatment and LT4 dose on the IQ score of patients with CH at 7 years was evaluated and reported that timing of treatment (<21 days) consider more important factor for IQ score.^[21]

In contrast, Kempers *et al.* in The Netherlands among Dutch CH patients have shown that advancing initiation

of treatment from 28 day to 20 day after birth did not result in improved cognitive or motor outcome in CH patients.^[22]

Considering previous studies in this field we could concluded that timing of treatment would have its positive effect on mental development if it initiated as earlier than 10-14 days after birth, i.e., as soon as it early diagnosis.

In current study, regarding to our screening guideline the levothyroxine starting dosage was 10 µg/kg/day, whereas recently high dose of 10-15 µg/kg/day is recommended in CH screening programs for proper results.^[23] It seems that treatment of patients with this recommended dose would increase the IQ score of patients and decreases the difference between patients and control group as reported by Simoneau-Roy in Qubec^[11] and Bongers-Schokking *et al.*^[24] Dubuis *et al.* showed that early high-dose therapy corrects the delay in CNS maturation related to intrauterine hypothyroidism. They emphasized on the importance of high dose treatment as therapeutic effect more than a replacement therapy.^[25] However, further studies is needed in this field.

Salerno *et al.* have indicated that high levothyroxine starting dose result in IQ improvement in CH patients even among those with severe form of the disease due to rapidly normalization of TSH level.^[26]

In PCH, there was a negative correlation between first screening TSH level and IQ score.

The definition of CH severity was not similar in different studies. Most of them defined it regarding to screening T4 and bone age, whereas we consider screening TSH for this purpose considering our previous findings in this regard. According to mentioned study, Iranpour *et al.* have indicated that CH patients with athyrosis had higher screening TSH level.^[27]

In this study, we did not evaluate the relation between different etiologies of CH, bone maturation, first T4 level, other factors related to the severity of CH, time of normalization of T4 and TSH and other environmental factors with IQ score, which considered as the limitations of the study. In addition, using other IQ measurement scores and large sample size would improve our achievements in this field.

In the study of Oerbeck *et al.* from studied variables, background (parental socioeconomic status, sex) and CH severity (serum T4 at diagnosis) were not associated with IQ, but treatment variables including levothyroxine starting dose and mean serum T4 during the first 2 years of treatment was significant predictors for verbal IQ.^[19]

In a recent study in Mexico there was not significant relationship between the severity of hypothyroidism ($P = 0.31$), age of initiation of treatment ($P = 0.271$) and etiology ($P = 0.127$) and IQ using Wechsler test.^[28]

Hsiao *et al.* in Taiwan evaluated the intellectual outcome of children with CH at 3-6 years of age using the Chinese fourth revision of the Binet-Simon scales and its association with variables such as CH etiology, age of treatment initiation, family socio-economic status, and severity of hypothyroidism. Mean of IQ was 102 ± 18.5 and it was significantly associated with the severity of hypothyroidism at diagnosis. Other variables did not affect the intellectual outcome significantly.^[29]

In summary, mean IQ score in both PCH and TCH patients are lower than control group in Isfahan, which were correlates negatively with treatment initiation time. We could conclude that though CH screening and early treatment has dramatically improved the prognosis of patients, we should try to optimize the outcome of CH screening. Considering that evidences and experiences in this field indicated that the most important treatment variables are high initial thyroxine dose of 10-15 µg/kg/d and timing of treatment, it is suggests that both early and high dose of treatment are required for normal developmental outcome in children with CH. In addition, further studies is needed with consideration of mentioned limitations for more appropriate results.

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