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Comparison of Intelligence Quotient in Early Treated Neonates with Congenital Hypothyroidism Compared to Healthy Children

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Abstract

Background: Congenital hypothyroidism (CH) is one of the preventable causes of intellectual disability. The aim of this study was to compare intelligence quotient (IQ) in early treated children with CH and healthy children.

Materials and Methods: This cohort study was conducted on 78 early treated children with CH (patient group) identified in screening program in Qazvin, Iran, started in 2006 and 90 age and sex matched healthy children (control group). The Persian version of Wechsler scale was performed to assess IQ (full scale, verbal, performance). Full-scale score among 70 and 80 were defined as borderline IQ and score among 50 and 69 were defined as mild mental retardation. Data were analyzed using SPSS software version 16.0.

Results: Mean age was 6.57±1.92 in patients group and 6.94±1.57 in control group (P>0.05). 46/78 of the patient group and 51/90 of the control group were male (P>0.05). Mean full scale (87.01±13.47 vs. 107.45±10.49; P< 0.001), verbal (85.73±13.54 vs. 106.86±10.18; P< 0.001), and performance (89.44±13.66 vs. 110.62±9.82; P< 0.001) IQ in the patients group were significantly lower than the control group. 73.1% of the patients group had average and above IQ. Borderline IQ (14.1% vs. 0) and mild mental retardation (12.8% vs. 1.1%, P<0.001) in the patients group were significantly higher than the control group (P<0.001).

Conclusion: Based on the results, although mean IQ in treated children with congenital hypothyroidism was lower than the control group, 73.1% of them had normal IQ. Early diagnosis and treatment of congenital hypothyroidism with high doses of thyroid hormone as well as patients' compliance can prevent mental retardation.

Key Words: Children, Congenital Hypothyroidism, Intelligence Tests, Thyroid Hormones.

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1- INTRODUCTION

Congenital hypothyroidism (CH) is the most common cause of mental retardation. Thyroid hormone is essential for the normal development of the central nervous system, especially from the beginning of the embryonic period to the end of the infancy period, which is a critical time for brain development. This fact led to the neonatal thyroid screening which began in 1975 in advanced countries and was followed by other countries in order for early diagnosis and treatment of CH (1-3). The goal of congenital thyroid screening programs is prevention of brain damage through early replacement therapy with thyroid hormone. Congenital hypothyroidism, if not treated can lead to severe intellectual disability, brain damage, cognitive and motor defects. Early diagnosis and treatment of CH by neonatal screening are effective in reducing the associated cognitive and behavioral damage (4). CH is the most common cause of curative mental retardation in the world and its prevalence is 1/3000 to 1/4000 live births (3, 5).

In Iran, the incidence of CH is 2 per 1,000 live births (6). Early diagnosis and timely treatment of CH can prevent this serious damage (7). Children who have thyroid stimulating hormone (TSH) values more than 200 mu/l may have developmental disorder in utero due to sever thyroid hormone deficiency (8, 9). Many studies have been designed to evaluate neurological disorders and determine the intelligence quotient (IQ) of children with CH (1, 2, 4, 7-10). Although IQ assessment studies in children diagnosed by screening have shown improvement in IQ scores, generally within the normal range (4), a number of studies have reported deficiencies in mental performance but this difference was not statistically significant (10). Some studies have reported behavioral and psychological disorders in children with CH (11, 12), and they have shown a 12-point decrease in IQ in CH children (13); while other studies did not show significant difference between affected children with early treatment as compared with healthy children (9). Various studies have shown that many factors affect the disease management and its consequences including the severity of CH, the initial thyroxine (T4) level, the time of treatment onset and dose of levothyroxine, the levels of TSH during treatment, the quality of treatment, and patient’s compliance (7). The average IQ score increased after screening program while before it was clearly less. Thyroid screening program was started in Qazvin city (Iran), in 2006 and is still ongoing; like other parts of Iran, congenital hypothyroidism is common in this province. This study was designed to compare IQ in early treated neonates with congenital hypothyroidism and healthy children.

2- MATERIALS AND METHODS

2-1. Study design and population

This prospective longitudinal study was conducted on early treated neonates with permanent congenital hypothyroidism in Qazvin province, Iran, in 2016.

2-2. Methods

The patients with CH and control group were evaluated for IQ at the age of 6 to 10 years. The patients were diagnosed through neonatal screening and later follow up. The control group was selected from children with normal thyroid function in kindergartens and elementary schools in Qazvin with the same socioeconomic condition and were matched for gender, age, and place of residence.

2-3. Neonatal screening

CH screening was begun 2006 in Qazvin province, Iran, and it is still going on. One drop of neonatal blood was collected on filter paper 3 to 5 days after birth and sent to the reference laboratory for review. If the TSH level was greater than 5 mIU/L the patient was recalled and the sample was taken again on filter paper. Neonates suspected of congenital hypothyroidism were referred to pediatric endocrinologist and those with low serum T4 (<6.5 µg/dl) and abnormal TSH (≥10 mIU/L) after the 28th day of birth were diagnosed as congenital hypothyroidism (1). Diagnosed neonates were treated with thyroid hormone at a dose of 10-15 µg/kg/day.

2-4. Follow-up

Patients were monitored by T4 and TSH measurements monthly for up to 6 months, every two months to one-year-old, and every 3 to 6 months until the end of the third year. At 3 years of age, the treatment was discontinued for 2-4 weeks and patients with elevated TSH (TSH≥ 10 mIU/L), and low levels of T4 (T4 < 6.5 µg/dl) who needed treatment with thyroid hormone after 3 years of age were considered as permanent congenital hypothyroidism. Children with thyroid agenesis in thyroid scan were also considered as permanent form (14).

2-5. Measurement

Patients' characteristics, such as the level of primary T4 and TSH, the age of treatment onset, gender, parental relationship, associated diseases, as well as treatment status during this period and thyroid scan were recorded. Study participants were examined with Iranian Wechsler Intelligence Scale for Children-Third Edition K-WISC-III, for 6-16 year old patients that includes13 subtests, 7 for performance IQ, and 6 for verbal IQ (15) or Persian Wechsler Preschool Scale (K-WIPSSI-III, for children 4-6 years of age) that includes 11 subscales with acceptable reliability and validity (16). These subtests can measure the Full Scale Intelligence Quotient (FIQ), a performance IQ (PIQ) and verbal IQ (VIQ). Verbal IQ evaluates information related to arithmetic, comprehension, vocabulary, and similarities; performance IQ evaluates the domain of (picture arrangement, geometric design, mazes, animal house and block design) and subtests. IQ score has a mean of 100 in normal population with a standard deviation (SD) of 15. A mean of 10 is considered for subtest scales with standard deviation of 3 (17). According to Wechsler Intelligence Scale for Children–Fifth Edition (WISC-V) IQ classification (18), IQ was classified as follows:130 and above is extremely high, 120-129 is very high, 110-119 is high average, 90-109 is average, 80-89 is a low average, and 70-79 is thought of as very low (borderline) and 50- 69 is graded as mild mental retardation (1,10,19).

2-6. Laboratory measurements

Follow- up thyroid function tests were performed in a single laboratory. Increase in TSH level more than 5 mIU/L during treatment ≥4 times was defined as insufficient control and less than 4 times was considered as relative control for CH (2).

2-7. Ethical consideration

The Ethics Committee of Qazvin University of Medical Sciences, Iran (28/20/8105) approved the study protocol. All parents gave written informed consent.

2-8. Inclusion and exclusion criteria

Inclusion criterion was diagnosis of permanent congenital hypothyroidism in National Neonatal Thyroid Screening Program during 2006-2011 that was confirmed by a pediatric endocrinologist. Patients with the history of underlying diseases that may affect IQ e.g. birth asphyxia and Down syndrome were excluded.

2-9. Data Analyses

Data were described as mean ± standard deviation (SD) or frequency (percentage). Categorical data were analyzed using Chisquare test. Continuous variables were compared using T-test. Correlation between IQ score and screening characteristics in patients with CH was assessed using Pearson's correlation coefficient. P-values less than 0.05 were considered as statistically significant. Data were analyzed using SPSS software for Windows (version 16) (SPSS Inc., Chicago, IL, USA).

3- RESULTS

Seventy-eight children with permanent CH and 90 matched healthy control subjects were entered into the study. Mean age was 6.47±1.69 years in patients group and 6.93±1.54 years in control group (P= 0.075). 46/78 of the patient group and 51/90 of the control group were male (P= 0.876). Mean age of treatment initiation was 13.20±4.81 days in the patient group. Twenty-three (29.5%) children in the patient group had ≥ 4 episodes of TSH values >5 mU/L. Only four patients had high or very high IQ. 56.6% of patients had relative control for CH. In thyroid scan, 54.2%, 28.8%, and 16.9% had normal thyroid/goiter, agenesis, and ectopic thyroid, respectively. Comparison of Intelligence quotient subscales between two groups are shown in **Table.1**. Mean full scale, verbal, and performance IQ in the patients group were significantly lower than the control group. 73.1% of the patients group had average and above IQ. Borderline IQ (14.1% vs. 0), and mild mental retardation (12.8% vs. 1.1%) in the patients group were significantly higher than the control group (P<0.001) (**Table.2**). Association of Intelligence quotient subscales in CH patients and treatment characteristics is shown in **Table.3**. Mean full scale, verbal, and performance IQ in the patients with relative control were significantly higher than the patients with insufficient control for CH. The IQ of infants treated before 21 days of birth was not significantly different from the IQ of those treated after 21 days. IQ score was not associated with gender and thyroid scan findings in CH patients. IQ score was not correlated with T4, TSH, and age at treatment onset (**Table.4**).

Table-1: Comparison of IQ scores between children with CH and control group.

IQ		CH patients	Control	P-value
Verbal	Male	85.56±15.32	105.43±10.61	< 0.001
	Female	85.96±10.69	108.74±9.39	< 0.001
	Total	85.73±13.54	106.86±10.18	< 0.001
Performance	Male	89.50±15.06	109.23±10.70	< 0.001
	Female	89.37±11.57	112.43±8.31	< 0.001
	Total	89.44±13.66	110.62±9.82	< 0.001
Full scale	Male	87.02±15.04	106.05±11.30	< 0.001
	Female	87.00±11.07	109.28±9.14	< 0.001
	Total	87.01±13.47	107.45±10.49	< 0.001

IQ: Intelligence quotient; CH: Congenital hypothyroidism.

Table-2: Comparison of IQ subscales between patients with CH and control group.

IQ		CH patients	Control group	P-value
Verbal	Average and above (≥ 90)	33 (42.3)	89 (98.9)	< 0.001
	Low average (80-89)	19 (24.4)	0	
	Borderline (70-79)	15 (19.2)	0	
	Mild mental retardation (50-69)	11 (14.1)	1 (1.1)	
Performance	Average and above (≥ 90)	40 (51.3)	89 (98.9)	< 0.001
	Low average (80-89)	21 (26.9)	0	
	Borderline (70-79)	10 (12.8)	0	
	Mild mental retardation (50-69)	7 (9.0)	1 (1.1)	
Full scale	Average and above (≥ 90)	38 (48.7)	89 (98.9)	< 0.001
	Low average (80-89)	19 (24.4)	0	
	Borderline (70-79)	11 (14.1)	0	
	Mild mental retardation (50-69)	10 (12.8)	1 (1.1)	

IQ: Intelligence quotient; CH: Congenital hypothyroidism.

Table-3: Association of baseline characteristics and IQ subscales in patients with CH.

Variable		IQ		
		Verbal	Performance	Full scale
Gender	Male	85.56±15.32	89.50±15.06	87.02±15.04
	Female	85.96±10.69	89.37±11.57	87.00±11.07
	P-value	0.898	0.969	0.994
Disease control	Relative	90.43±13.87	94.03±14.11	91.80±14.16
	Insufficient	82.00±14.73	85.56±14.99	82.95±14.01
	P-value	0.038	0.040	0.028
Age at treatment onset	< 21 days	86.64±14.16	90.22±14.38	87.80±14.16
	> 21 days	76.80±10.80	80.20±10.13	78.40±9.28
	P-value	0.136	0.134	0.152
Thyroid scan	Dyshormonogenesis	84.78±16.17	88.09±15.66	86.00±16.22
	Agenesis	87.76±14.00	90.88±15.26	88.17±13.39
	Ectopic Thyroid	88.00±7.67	93.40±8.03	90.30±8.13
	P-value	0.721	0.569	0.687

IQ: Intelligence quotient; CH: Congenital hypothyroidism.

Table-4: Correlation of IQ score and screening characteristics in patients with CH.

Variables	IQ	
	r	P-value
T4	-0.027	0.833
TSH	0.157	0.224
Age at treatment onset	-0.039	0.762

IQ: Intelligence quotient; CH: Congenital hypothyroidism, r: Pearson correlation coefficient.

4- DISCUSSION

The aim of this study was to compare IQ in early treated neonates with congenital hypothyroidism and healthy children in Qazvin province, Iran. In the present study, mean IQ scores in the patients with CH were in normal range but significantly lower than the control group. IQ score was not correlated with T4, TSH, and age at treatment onset. The majority (85%) of our patients had T4 in the upper half of normal range and TSH values were within the ranges of 0.5 -2 mU/L as the Rose et al. recommendations during treatment (14). IQ score was not associated with gender, age at treatment onset, and thyroid scan findings in CH patients. Congenital hypothyroidism adults who were born before starting the screening program had cognitive and motor deficits in both verbal and performance domains. CNS damage was more common in persons with severe CH (20). Congenital hypothyroidism is the most common cause of preventable neurodevelopmental delay (10). Therefore, CH screening programs have been administered in many countries in order to prevent the related mental retardation. The purpose of early treatment of CH is to minimize the exposure of central nervous system to decreased thyroid hormones (21). However, the results of studies on the success of early treatment on intelligence quotient are inconsistent because it depends not only on early diagnosis but also on many other factors including T4 and TSH levels at diagnosis, patients' compliance and starting dose of levothyroxine. On the other hand, the patients had neurodevelopmental defect even with early and appropriate treatment, which might be due to decreased thyroid hormone during the perinatal and early neonatal period (1). Najmi et al. in a study in Isfahan, Iran, found that although the mean score of IQ in patients with CH was in normal range, it was significantly lower than control group (1). In another study in 5 provinces of Iran, mean IQs of 240 children with CH at the age of 6 years was lower than their healthy controls (22). In Dimitropoulos et al.'s study in Switzerland, the Wechsler Intelligence Scale for Children was performed for children with CH at age of 14 years and their Full-scale IQ score was significantly lower than controls after adjustment for socioeconomic status and gender (101.7 vs. 111.4) (2). In Bongers-Schokking et al.'s study on 45 patients and 37 control children in Netherlands, IQ Scores and the seven subtests of the children with CH did not differ significantly from the control group (104.7 ± 16.2 vs. 105.0 ±15.8) using the short version of the revised Amsterdam child intelligence test (Rakit) (23). Lower initial thyroxine (T4) levels was correlated with poorer IQ (r=0.27, p=0.04) in Dimitropoulos et al.'s study (2). Elrabie Ahmed et al. have reported a negative correlation between TSH level and IQ score in patients with CH (24). In Najmi et al.'s study, TSH level and timing of treatment in permanent group had negative correlation with IQ score (1). In Kempers et al.'s study on children with CH at 10 years of age, there was no correlation between starting day and T4 dose with IQ score (12). However, in a study by Seo et al., the initial fT4 level had positive correlation with the Full Scale IQ score (10). In the present study, 73.1% of the patients group had normal IQ. Borderline IQ and mild mental retardation in the patients group were significantly higher than the control group ($P<0.001$). However, in Rahmani et al.'s study, none of the treated children with CH had IQ less than 70 (22). In Seo et al.'s study, IQ scores of 5 to 7 year old children with early treated CH were also within normal range, but they did not compare the results with control group (10). In a study by Kim and Lee in Korea, IQ scores in all patients with CH were in normal range (25).

Dimitropoulos et al. found that mean IQ scores at 14 years old were in the normal range after early high dose treatment in patients with CH, but significantly lower than the control group; 21% of children with CH had IQ less than -2SD below mean IQ of the controls in their study (2). In Grüters et al.'s study in Berlin, 92% of early treated children with CH had normal scores for the IQ and developmental quotients at aged 2–16 years old (26). Mean full scale, verbal, and performance IQ in the patients with relative control were significantly higher than the patients with insufficient control in the present study. Dimitropoulos et al. did not find an association between endocrine levels in childhood or between under treatment and intellectual impairment (2). Previous studies have shown a correlation between the time of treatment onset and intellectual outcome. Hulse and MacFaul et al. showed that if treatment was begun before age 6 weeks, CH children would achieve normal growth and intelligence (27, 28). In Seo et al.'s study IQ scores were not significantly different between agenesis and other etiology of CH (10). In Dimitropoulos et al.'s study, IQ scores in the thyroid agenesis and dysgenesis groups were lower than controls. On the other hand, the agenesis group and the dysgenesis group were only different in the Performance IQ score (2). In Boileau et al.'s study in France, the IQ of CH patients treated after 21 days were significantly lower than control group whereas the IQ of CH patients treated before 21 days were not different from the control group and they concluded that treatment onset seems to be an important predictor for the intellectual outcome (29). In Selva et al.'s study, there was negative and significant correlation between verbal IQ and full scale IQ with age of treatment onset in children with transient CH (21).

4-1. Limitations of the study

The present study had some strengths including treatment of patients by a single pediatric endocrinologist and performing follow up thyroid function tests in a single laboratory. Environmental factors including maternal education and parental occupation may have an effect on IQ but it was not evaluated in the present study. The association of IQ score with time of normalization of T4 and TSH was also not assessed.

5- CONCLUSION

Although mean IQ in treated children with congenital hypothyroidism was lower than the control group, 73.1% of them had normal IQ. Early diagnosis and treatment of congenital hypothyroidism with high doses of thyroid hormone as well as patients' compliance can prevent mental retardation. However, developmental disorder in fetus due to sever thyroid hormone deficiency in embryonic period is irreversible and cannot be prevented by neonatal screening and early treatment.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENTS

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