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COMPARISON OF IQ BETWEEN PATIENTS WITH TREATED CONGENITAL HYPOTHYROIDISM AND HEALTHY CHILDREN IN THE KURDISH POPULATION - A HISTORICAL COHORT

S. Nili[1], E. Ghaderi[2], N. Ghotbi[2], F. Vafai Baneh[3,*]

Kurdistan University of Medical Sciences - [1]Disease Prevention, [2]Center for Social Determinants of Health, [3]Mental Health Department of Mental and Social Health and Addiction, Sanandaj, Islamic Republic of Iran

Abstract

Background. Prevalence of congenital hypothyroidism is about one per 414 live births in Kurdistan Province, a western province in Iran. Recently, a surveillance system (diagnosis, report and treatment) was developed to control the disease in Iran.

Aim. This study aimed to compare the IQ of children with congenital hypothyroidism with normal children in this province, where the disease is highly prevalent.

Subjects and Methods. This retrospective cohort study was conducted on 100 children with congenital hypothyroidism under continuous treatment with thyroxine and a group of 100 healthy infants. Two tests of Goodenough draw-a-man test and Proteus Mazes were used to measure IQ. Statistical analysis was done by SPSS 16 and multiple regression.

Results. The average IQ of the patient group treated for 42 months with thyroxine and healthy group were 103.4 (±16.9) and 103.4 (±15.4), respectively (p=0.989). There was no statistically significant difference between the IQ of children with transient and permanent hypothyroidism. In multivariate analysis, the only effective factor on IQ was mothers' education.

Conclusion. There was no statistically significant difference between the IQ of children with congenital hypothyroidism who have been treated with thyroxine and the IQ of healthy children. So, there is appropriate quality of care for patients who are living in this province where the disease is highly prevalent.

Key words: congenital, hypothyroidism, mental retardation, Iran.

INTRODUCTION

Congenital hypothyroidism (CH) is one of the major preventable causes of mental retardation which has no symptoms at birth. The disease may be due to different factors including: disorders in partial or complete development of thyroid glands, dysfunctions caused by inappropriate thyroid replacement in fetus (Ectopic Gland), iodine deficiency in residential area, use of certain drugs such as anti-thyroid drugs by pregnant women, and hereditary disorders resulting in inability in making thyroid hormones(1-5).

According to national iodine deficiency control program in Iran, iodine added to salt that can be taken with food but supplement to pregnant women or other groups not provided. Also pregnant women not evaluated about thyroid function, routinely. So it is probable that in iodine deficiency area, hypothyroidism in newborn was prevalent.

The prevalence of CH varies in different regions. The disease prevalence has been reported to be one per 1000 live births in France (6), one per 800 live births in Greece (7), one per 2372 live births in the United States of America (8), and one per 2640 live births in India (9).

In Iran, several studies conducted about prevalence of CH (10-12), so that the prevalence of disease has been reported to be one per 1000 live births in Tehran, one per 370 live births in Isfahan (13-14), one per 303 live births in Kashan (15) and one per 1433 live births in Shiraz (11). In Kurdistan Province, a western province in Iran which is located in a mountainous region, the population is mainly from Kurd ethnicity and the prevalence of the disease is about one per 414 live births (16). About 51.8% of students had urine iodine level less than 9.7mcg/dL (Iodine deficiency) in recent survey in Kurdistan province.

The first screening program for congenital hypothyroidism diseases in large populations was carried out in Quebec, Canada in 1974. Nowadays, congenital hypothyroidism disease screening programs are conducted systemically in industrialized countries (17). In Iran, congenital hypothyroidism screening program has been started since September 2005 by the

*Correspondence to: Farogh Vafai Baneh MD, Kurdistan University of Medical Sciences, Mental Health Department of Mental and Social Health and Addiction, Health deputy, Abidar Ave, Sanandaj, Kurdistan, 6618634683, Islamic Republic of Iran, E-mail: fwafaei@yahoo.com

Ministry of Health and Medical Education and it was carried out in the country by the health care system (18). Early diagnosis and treatment of disease prevents brain disorders in neonates with hypothyroidism. The average IQ of patients with congenital hypothyroidism was 76 before screening program, however, after treatment it increased to 104 which was comparable to the IQ score of normal children which was 106 (19).

Since preventing the loss of IQ is a key indicator in assessing neonatal hypothyroidism screening program, and as Kurdistan Province is one of the high-risk provinces in the world with a high prevalence of disease, appropriate administration of the program and suitable treatment are of great importance. This study aimed to compare the IQ of children with congenital hypothyroidism with that of healthy children in this province, where the disease is highly prevalent. The results can determine the quality of care for these patients.

MATERIALS AND METHODS

Participants

This retrospective cohort study was conducted on neonates with congenital hypothyroidism (exposure group) and also a group of screened healthy infants (non-exposure group). In the program of screening neonatal hypothyroidism, on the third to the fifth day after birth few drops of blood are obtained from the heel of newborn by a Lancet and are poured on a filter paper; after drying, which usually takes three hours, they are sent to newborn screening laboratories in the center of provinces through express post. After conducting tests and measuring TSH level, newborns with a TSH level of less than 5 mU/L are diagnosed as healthy, otherwise the suspected cases are called for further tests. When TSH level is from 5 to 9.9, second paper filters are taken; however, when TSH level is more than 10, newborns shall be referred to focal points for serum tests to prove or reject the disease. The ideal time to start treatment is from about the second week to the third week after birth. Treatment of patients starts with doses of 10 to 15 μg/kg of levothyroxine. After three years of treatment, to determine whether the disease is transient or permanent, the treatment for patients is discontinued for two to four weeks, and the tests are repeated. In the case of achieving normal results in the tests, it can be concluded that the disease is transient and the treatment must be discontinued; otherwise, the disease is permanent and the patient must take drugs until the end of life (20).

Congenital hypothyroidism screening program in Iran has been incorporated all over the country since 2005. Data of patients and other screened neonate are registered in each city and the special forms designed for this program are the same all over the country and they are completed on a regular basis. In this study, children with congenital hypothyroidism who had been detected and treated from the beginning of the program and were more than 42 months of age, were selected as the exposed group through census sampling. The same number of children of the same sex, the same age, and from the same region who had normal hypothyroidism screening test was enrolled in the study as the unexposed group.

The study was approved by the ethics committee of Kurdistan University of Medical Sciences. After selecting the participants, their parents were contacted and after explaining the objectives of the study, parents were asked to allow the researchers to visit them at their home. Before visiting them at home, patient's records were reviewed and the required data were recorded to correct the defects. Then a blinded psychologist visited patients' homes and the evaluated IQ as main outcome.

Measurement tools

To measure IQ in both groups of participants, the two tests of Goodenough draw-a-man test and Proteus Mazes were used. All tests in both groups of participants were conducted by one psychologist.

Goodenough Draw-a-man test is used for children 3 years to 15 years old. To score the drawing 51 items must be assessed one by one in the painting; one score is given for every observed item and then the table of scores is used to calculate child's mental age. Reliability of the majority of signs in Goodenough draw-a-man test has been above 80% (21-22). The correlation coefficient for IQ is 0.83 for interscorer reliability and 0.92 for intrascorer reliability(23-24). The test retest coefficients on children four to eight years old, with an interval of two to three weeks, have been reported to be from 53% to 87% (25).

Proteus mazes are a simple tool to assess nonverbal intelligence, planning capacity, visual and motor coordination, and the perceptual organization of an individual. In this study, Proteus mazes types 1965 which have 13 mazes were used. The scores of this test are significantly correlated with test scores of planning item in Wisconsin card sorting test and TAT test (26). Cronbach's alpha coefficient for this test has been reported as 81% (27). There is no time limitation for executing this test. Child's IQ is calculated using

a table which is provided to standardize this test. Goodenough draw a man test and Proteus mazes test have a correlation between 25% and 27% (28).

Statistical Analysis

After collecting the data, they were entered into SPSS 11.5 software. Chi-square and Fisher's exact test were used to compare qualitative variables between the two groups of the study and independent t test was used for comparing quantitative values. Then, to determine the factors affecting IQ, multiple regressions test was used. The significance level of less than 0.25 in the univariate analysis was considered as the inclusion criteria to enter variables into regression model. Two regression models were designed: The first one was to evaluate the effect of hypothyroidism on IQ while controlling potential confounders and the second one was to evaluate the effect of the type of hypothyroidism on IQ while controlling potential confounding factors. When hypothyroidism has an impact on IQ, it indicates the difficulty in treating patients and in their medical instructions.

RESULTS

In this study 100 children with congenital hypothyroidism and 100 healthy children were studied. A total of 53 patients (53%) of those with hypothyroidism were male and the rest were female; 26 patients (26%) were from rural areas. Of all, 28 patients (28%) in congenital hypothyroidism group and 33 children (33%) in the healthy children group were born through caesarean. Seven patients (7%) in congenital hypothyroidism group and five children (5%) in the healthy children group had a family history of mental retardation; 12 patients (12%) in congenital hypothyroidism group and six children (6%) in the healthy children group were left handed which showed no significant statistical difference. A total of 45 mothers of healthy children (45%) and 62 mothers of patients (62%) were illiterate or were at primary education level (p=0.025).

The mean birth weight was 3123.3 gram (±512.1) in patients and 3226.5 gram (±453.8) in the healthy children group (p=0.133). The mean birth height was 49.8 centimetres (±2.5) in the patient group and 50 (±2.3) centimetres in the healthy children group (p=459). In terms of IQ, the average IQ of the patient group was 103.4 (±16.9) and the average IQ of the healthy children group was 103.4 (±15.4), so the difference was not statistically significant (p=0.989) (Table 1). Prevalence of IQ<85 in patient group and healthy children were 7% and 14% respectively but this difference was not statistically significant (p=0.106).

Table 1. Comparison of study's variable between normal and congenital hypothyroid groups

Variable	Normal	Congenital Hypothyroid	P_value
Weight in newborn	3226.5 (±453.8)	3123.3 (±512.1)	0.133
Height (cm)	50 (±2.3)	49.8 (±2.5)	0.459
Mother's Education (level)			
Illiterate and Primary	45 (45%)	62 (62%)	
High school	26 (26%)	23 (23%)	0.025
Diploma and college	29 (29%)	15 (15%)	
Head Circumference	34.6 (±1.5)	34.6 (±1.4)	0.920
Delivery			
NVD	67 (67%)	72 (72%)	0.443
C.S	33 (33%)	28 (28%)	
Family relation of parents	17 (17%)	24 (24%)	0.220
History of Mental Retard in the Family	5 (5%)	7 (7%)	0.552
Breast feeding	95 (95%)	94 (94%)	0.756
Left Handedness	6 (6%)	12 (12%)	0.138
Smoking			
Active	5 (5%)	2 (2%)	
Passive	24 (24%)	23 (23%)	0.492
No	71 (71%)	75 (75%)	
Birth Order	1 (1-6)	2 (1-6)	0.008
Family Income (Thousand Tomans)	500 (150-4500)	500 (100-5000)	0.173
Preschool	32 (32%)	21 (21%)	0.109
Mother's age	26.5 (±5.1)	27.8 (±6.2)	0.125
Father's Age	30.6 (±5.3)	32.9 (±7.3)	0.010
Mean age of treatment (day)	-	18.4(±10.45)	-
Mean IQ	103.4 (±15.4)	103.4 (±16.9)	0.989

Table 2. Comparison of study's variable between permanent and transient congenital hypothyroid groups

Variable	Transient congenital hypothyroid	Permanent congenital hypothyroid	P_value
Sex			
Male	38 (54.3%)	15 (50%)	0.694
Female	32 (45.7%)	15 (50%)	
Mother's Education (level)			
Illiterate and Primary	48 (68.6%)	16 (46.7%)	
High school	13 (18.6%)	10 (33.3%)	0.115
Diploma and college	9 (12.9%)	6 (20%)	
Residency			
Urban	48 (68.6%)	26 (86.7%)	0.081
Rural	22 (31.4%)	4 (13.3%)	
Newborn's Weight	3097.1 (±484.6)	3184.3 (±575.5)	0.438
Height (cm)	49.4 (±2.4)	50.6 (±2.7)	0.039
Head Circumference (cm)	34.8 (±1.4)	34 (±1)	0.082
Delivery			
NVD	51 (72.9%)	21 (70%)	0.771
C.S	19 (27.1%)	9 (30%)	
Family relation of parents	17 (24.3%)	7 (23.3%)	0.919
History of Mental Retards in the Family	4 (5.7%)	3 (10%)	0.425
Breast feeding	68 (97.1%)	26 (86.7%)	0.064
Left Handedness	8 (11.4%)	4 (13.3%)	0.749
Smoking			
Active	1 (1.4%)	1 (3.3%)	
Passive	15 (21.4%)	8 (26.7%)	0.679
No	54 (77.1%)	21 (70%)	
Birth Order	2 (1-5)	1 (1-6)	0.010
Family Income (thousand Tomans)	500 (100-1000)	500 (200-5000)	0.415
Preschool	11 (15.7%)	10 (33.3%)	0.047
Mother's age (years)	28.1 (±6.3)	27.1 (±6.3)	0.454
Father's Age (years)	33.3 (±6.4)	32 (±8.6)	0.421
Mean IQ	102.6 (±16.5)	105.5 (±17.9)	0.423
Serum TSH (mU/L)	28.1 (±24.8)	75.8 (± 78)	0.008
T4 (ug/dL)	6.8 (±6.2)	7.5 (±6.8)	0.654

A total of 70 patients (70%) were suffering from permanent congenital hypothyroidism. The Birth ranking of patients with transient hypothyroidism was higher than those with permanent hypothyroidism. There was no statistically significant difference between the IQ of children with transient and permanent hypothyroidism. The mean serum TSH was 28.1 (±24.8) mU/L in patients with transient hypothyroidism and 75.8 (±78) mU/L in patients with permanent hypothyroidism (p=0.008), however there was no statistically significant difference between T4 concentrations in the two groups (Table 2).

Table 3 shows that the presence of hypothyroidism did not affect the IQ of children with congenital hypothyroidism compared with the IQ of healthy children. The only effective factor was mothers' education, so that the literacy of mothers increased children's IQ. Moreover, there was no difference between the IQ of people with permanent and transient congenital hypothyroidism, nevertheless mothers' age and mother's literacy was associated with higher IQ.

DISCUSSION

The results showed that there was no statistically significant difference between the IQ of children with congenital hypothyroidism who were treated and the IQ of healthy children. Additionally, there was no significant difference between the IQ of people with permanent and transient congenital hypothyroidism. It can be said that there is appropriate quality of care for patients who are living in this province where the disease is highly prevalent. In this study the underlying factors that can affect IQ were also controlled to assess the effects of treatment better.

Physicians use a variety of treatment methods for children with congenital hypothyroidism. Although, national guidelines have set some instructions to control all patients in a focal point, it is likely that a change would be made in treatment before referring

Table 3. Multiple Regression model for the evaluation of relation between Hypothyroidism and IQ

Variables	Unstandardized Coefficients		Standardized Coefficients	t	P_ Value	95% Confidence Interval for Beta	
	Beta	Std. Error	Beta			Lower Bound	Upper Bound
Constant	75.813	26.455	-	2.866	0.005	23.599	128.027
Hypothyroid	1.119	2.481	0.034	0.451	0.652	-3.777	6.016
Literacy of Mother	9.259	2.675	0.281	3.461	0.001	3.978	14.539
Left Handedness	2.888	4.571	0.047	0.632	0.528	-6.133	11.909
Mother's Age	0.190	0.279	0.065	0.681	0.497	-0.361	0.741
Birth Order	-0.504	1.542	-0.032	-0.327	0.744	-3.548	2.540
Family Income (logarithm)	3.187	4.777	0.052	0.667	0.506	-6.242	12.616
Constant	117.982	48.903	-	2.413	0.018	20.519	215.446
Literacy of Mother	14.161	4.617	0.381	3.067	0.003	4.958	23.363
Mother's Age	1.079	0.457	0.364	2.362	0.021	0.169	1.990
Birth Order	-3.531	2.433	-0.221	-1.451	0.151	-8.381	1.319
Family Income (logarithm)	-7.876	9.234	-0.107	-0.853	0.396	-26.280	10.527
Type of Hypothyroidism	1.277	5.116	0.031	0.249	0.804	-8.921	11.474
Serum TSH	0.021	0.043	0.059	0.490	0.626	-0.065	0.107

Model 1 (R2=0.092) shows that the presence of hypothyroidism did not affect the IQ of children with congenital hypothyroidism compared with the IQ of healthy children. The only effective factor was mothers' education, so that the literacy of mothers increased children's IQ. Model 2 (R2=0.188) shows that there was no difference between the IQ of people with permanent and transient congenital hypothyroidism, nevertheless mothers' age and mother's literacy was associated with higher IQ.

to the focal point which may adversely affect IQ. The best level of IQ is achieved only when the treatment of infant is initiated on-time and early and appropriate metabolic controls is sustained throughout the duration of treatment; this is possible only when the treatment is carried out fully based on national protocols.

In this study, the average IQ of the patient group and healthy group were 103.4 (±16.9) and 103.4 (±15.4%), respectively, and therefore no statistically significant difference was observed (p=0.989); other studies have obtained similar results (29-31). However, according to the results of a study, after adjusting socioeconomic status and sex, IQ score of patients was significantly lower than that of the control group (101.7 vs. 111.7 and P <0.0001) (32).

Mothers of congenital hypothyroidism children have lower level of literacy than no exposed group in univariate analysis (Table 1); so level's education may be associated with nutritional factors or other risk factors of CH. Since IQ of children may associate with mother's literacy level, we controlled probable confounding effect of it on IQ with multivariate analysis. In this study, there was no significant relationship between the IQ of children with transient or permanent types of congenital hypothyroidism. However, in a study, the mean verbal, non-verbal, and total IQ of control group was significantly higher than those in both groups of patients with transient or permanent hypothyroidism. In patients with permanent hypothyroidism, there was a negative relationship between verbal, non-verbal, and total IQ with TSH and starting age of treatment. In patients with transient hypothyroidism there was a significant negative relationship between verbal IQ (r = -0.4) and total IQ (r = -0.38) with the starting age of treatment (r = -0.46) (33). In another studies, total, verbal, and non-verbal IQ among people with transient type were lower than those among normal people (78.3±11.1 *versus* 90.9±14.2; p<0.05, 84.4±15.4 *versus* 96.2±14.8 (p>0.05), and 75±8.5 *versus* 89.2±12.5 (P<0.01) (34-35).

In this study, there was no relationship between the TSH and T4 levels and IQ scores, which is similar to the results of other studies (36). However, according to a study, patients with severe congenital hypothyroidism had lower total, verbal, and non-verbal IQ scores than healthy subjects, while patients with mild and moderate congenital hypothyroidism were comparable with the normal population (37). According to some other studies, T4 levels had an impact on IQ scores of patients with congenital hypothyroidism (38-39).

The patients, who were assessed in this study, started their treatment with doses of 10 to 15µg/kg/day and the result was to maintain a normal IQ. This is also confirmed by other studies (35-36, 39). In this study, following the national protocols, treatment was started prior to 28th days of age and therefore infant hypothyroidism did not have a significant negative effect on newborns' IQ; similar results have been observed in other studies, as well (35-37, 40).

Other studies noted the positive effects of starting treatment before the 21st days of age which rises IQ scores (38). In addition, in a research conducted

by Rovet *et al.* (41), psychometric tests were used for children 6.4 kg/day with a dose of 9 µg/kg/day. Verbal IQ was 98.6 *versus* 106.3 IQ (P<0.01), non-verbal IQ was 103.8 *versus* 108.2 (P>0.05), and total IQ was 100 *versus* 107.6 (P<0.01), respectively. Selva *et al.* (42) provided a report on regional screening program in North West America and showed that the IQ of children who begin treatment with levothyroxine with a dosage of 50 µg/kg/day had about 11 grade of IQ higher than others. It can be concluded that, the quality of treatment in Kurdistan is appropriate, and practitioners appropriately follow the recommended dosage and starting time of treatment. One of the strengths of our study was that we assessed all possible items that might be a confounding factor while assessing the effects of hypothyroidism on IQ. Therefore we examined the effect of other factors on IQ.

This study also had some limitations. Unfortunately, due to immigration and changes in their locations and addresses, it was not possible to access all patients diagnosed with hypothyroidism (130 patients) and only 100 were available.

In conclusion, there was no statistically significant difference between the IQ of children with congenital hypothyroidism who were treated and the IQ of healthy children. So, there is appropriate quality of care for patients who are living in this province where the disease is highly prevalent.

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Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

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