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Comparison of Intelligence Quotient between Permanent Congenital Hypothyroid Children and Healthy Children

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Abstract

Background: Congenital hypothyroidism (CH) is the most common curable cause of mental retardation. The aim of this study was to compare the intelligence quotient (IQ) of congenital hypothyroid patients with that of healthy children.

Methods: This case-control cross-sectional study was performed on 30 permanent CH children within the age range of 6-12 years referring to the Endocrine Clinic of Imam Reza Hospital, Mashhad, Iran between April 2017-2019. In addition, 32 healthy children of the same age and gender from the family members of the patients were chosen as the control group. The intelligence test was performed using the revised version of the Wechsler Intelligence Scale for Children and the mean verbal, performance, and total IQ were compared between case and control groups.

Results: There was no significant difference between the two groups in terms of age and gender. The mean verbal, performance, and total IQ in the case group were obtained as 104.33±13.30, 93.13±7.42, and 98.03±7.94, respectively. With regard to the healthy group, these mean values were, respectively, estimated at 121.34±16.74, 99.65±11.92, and 110.71±14.15 (the normal range of IQ was 90-109).

Accordingly, the results revealed a significant difference between the two groups in terms of verbal (P=0.000), performance (P=0.013), and total (P=0.000) IQ. Furthermore, a relationship was found between early treatment initiation and higher verbal IQ (r=0.521; P=0.032), as well as between lower thyroid-stimulating hormone and higher performance IQ (r=0.559; P=0.020).

Conclusion: The permanent CH children that had received timely treatment had normal levels of IQ based on the Wechsler Intelligence test. However, it was significantly lower in the CH children than that in healthy children of the same age, gender, and socioeconomic status.

Key Words: Congenital hypothyroidism, Intelligence test, Neonatal screening.

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1- INTRODUCTION

Thyroid hormones are essential for the maturation of the central nervous system, especially from the early stages of fetal life up to 2-3 years of age (1). Congenital hypothyroidism is one of the most common diseases leading to neurodevelopmental disorders. However, the timely diagnosis and treatment of this condition can prevent the incidence of this important complication and many other problems (2, 3). The incidence of congenital hypothyroidism among neonates varies across different countries and ranges from 1:2000 to 1:4000 (4, 5). The worldwide prevalence of this condition based on the screening tests was initially reported as 1:4000. During the last two decades, the prevalence of this deficiency has reached 1:2000, probably due to the diagnosis of milder cases of the disease (1). According to the evidence, congenital hypothyroidism is more common in Iran (4, 6-8).

Implementation of the CH neonatal screening program has improved cognitive outcome (9). Similar to other cities in Iran, the national program of neonate screening was established in Mashhad in 2004-2005 (10). The evaluation of the efficacy and effectiveness of this program in reducing the complications of congenital hypothyroidism is a necessary measure. There are inconsistent results on the neurodevelopment of children with congenital hypothyroidism receiving timely diagnosis and treatment (11, 12). Intelligence quotient (IQ) is the most common scale for evaluating mental development. Some studies showed lower IQ levels and cognitive deficits in CH children. However, some other studies demonstrated that CH children have the same mental development and IQ level as controls (13). Regarding this, the present study was conducted to evaluate and compare IQ between congenital hypothyroid pediatric patients and healthy children using the revised version of the Wechsler Intelligence Scale for Children.

2- MATERIALS and Methods

2-1. Study design and population

This two-group cross-sectional study was performed on permanent congenital hypothyroid children within the age range of 6-12 years referring to the Endocrine and Metabolism Clinic of Imam Reza Hospital, Mashhad, Iran, and a control group between April 2017 and April 2019. For each CH case, a healthy first- or second-degree family member of the same age and gender was selected as the control group. The selection of the control group in this way has eliminated the influence of socioeconomic and genetic factors.

2-2. Methods

According to the hypothyroid screening protocol, the thyroid-stimulating hormone (TSH) was measured by a heel-prick filter paper in the neonates referred at 3-5 days of age (14). The neonates with abnormal screening results were re-tested, and those with abnormal T4 and TSH (TSH>10 and T4<6.5) were identified as congenital hypothyroidism and followed up regularly (14).

Hypothyroid neonates had been treated with levothyroxine tablets (made in Iran) at a dose of 10-15 mcg/kg/day as soon as the diagnosis.

CH can be classified into permanent and transient types (15). They were controlled every month during the first 6 months and then every 3 months up to 2 years of age, and every 6 months thereafter. For the determination of permanent and transient congenital hypothyroidism, TSH and T4 concentrations were measured for patients at 3 years of age, 4 weeks after the discontinuation of levothyroxine. The patients with elevated TSH levels (above 10 mu/L) and decreased T4 levels (T4<6.5) were known as permanent hypothyroidism.

The parents of the children (both case and control groups) were contacted by telephone and provided with necessary explanations about the research project. After obtaining parental informed consent, the children were entered into the study. Subsequently, necessary arrangements were made to perform the intelligence test. Other information needed (e.g., age, gender, birth weight, height, and head circumference, current weight and height, TSH level at the onset of the treatment, age at the onset of the treatment, etiology of congenital hypothyroidism, weight and height progression, development and frequency of TSH elevation) were obtained from previously recorded data in the medical records or by questioning from the mothers.

2-3. Measuring tools: validity and reliability

The revised version of the Wechsler Intelligence Scale for Children, which was standardized in Iran with acceptable reliability and validity, was used to assess intelligence of the children. This test consists of verbal and performance IQ subscales, which form the total IQ. The Wechsler's IQ score is categorized as < 69 (extremely low), 70-79 (borderline), 80-89 (low average), 90-109 (average), 110-119 (high average), 120-129 (superior), and > 130 (genius) (16, 17). The etiology of congenital hyperthyroidism was known by thyroid scan or ultrasound findings, which consisted of dysgenesis, ectopy, hypoplasia, athyreosis, and dyshormonogenesis.

Reliability: Internal consistency coefficients across the nine age groups were reported as .95–.96 for the FSIQ and ranged from .85 to .96 for index scores and from .71 to .95 for the subtest scores. Stability coefficients (uncorrected) for all ages were .88 for the FSIQ, .78–.88 for index scores, and .69–.81 for the subtests. Corrected coefficients were slightly higher. Also the overall interscorer agreement was very high (.98–.99)

Validity: Consistent with Standards for Educational and Psychological Testing (American Educational Research Association [AERA], American Psychological Association [APA], & National Council on Measurement in Education [NCME], 1999), evidence for validity was structured around areas of test content, response processes, internal structure, relations with other variables, and consequences of testing. As anticipated, subtest inter-correlations were all positive for both age bands and reflected Spearman's (1904) positive manifold and measurement of general intelligence (g). Factor index score inter-correlations were also moderately high for both age bands as observed in other Wechsler scales and intelligence tests in general (18).

Reliability of the Persian version of the test, based on internal consistency for all 11 age groups: full scale (96%), verbal scale (94%) and nonverbal scale (90%). Based on review validity: full scale (95%), verbal scale (93%) and non-verbal scale (90%). This review was one month apart. It showed more reliability in the 2 years interval.

Validity of the Persian version of the test:It was found to be correlated with the fourth revision of Stanford Binet (0.78), Peabody Individual Achievement Test (0.71), K-ABC (0.70), and the group intelligence tests (0.66). (17)

2-4. Intervention

In order to examine child development, three components of sitting, walking, and speaking time were considered. According to the Denver II scale, the appropriate time points for sitting, walking, and talking are about 6-8, 12-15, and 12-18 months of age, respectively. Each child's height and weight were also recorded in written files, and CDC growth charts were used to

measure height and weight progression. The current weight and height of the control group were also respectively measured by the use of scales and meters in the clinic. In addition, birth weight, length, and head circumference were measured using the growth cards or asking from the mothers. The IQ (i.e., verbal, practical, and total IQ) of the children in the case and control groups was assessed by a senior psychologist using the Wechsler Intelligence test at the clinic of Imam Reza Hospital.

2-5. Ethical consideration

This study was approved by the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran with the ethical code of IR.MUMS.fm.IEC.1395.651.

2-6. Inclusion and exclusion criteria

The minimum sample size was estimated as 25 cases in each group considering α of 0.05 and β of 0.1 using the PASS software. The case group consisted of 30 under-treatment permanent congenital hypothyroid children, detected by neonatal screening without any other abnormalities (e.g., history of meningitis, febrile convulsion, head trauma, severe neonatal jaundice, and blood exchange) or associated anomalies (e.g., auditory, renal, or central nervous system disorders, chromosomal abnormalities, and genetic syndromes).

The inclusion criteria were: 1) birth after an uncomplicated pregnancy, 2) singleton pregnancy, and 3) good compliance. More than 10 times TSH rise was considered as poor compliance. On the other hand, the exclusion criteria were: 1) parental dissatisfaction, 2) lack of cooperation in performing intelligence tests, and 3) no matched child in the family to be used as a control. The case group was compared with a healthy control group consisting of 32 healthy children aged 6-12 years. In order to eliminate the effect of environmental, social, and genetic factors, the control group was selected from the patient's family members (i.e., the first- or second -degree relatives of the sick children) who were matched in terms of age, gender, and socioeconomic status.

2-7. Data Analyses

The data were analyzed in SPSS software (version 16). The comparison of the normally distributed quantitative data between the two groups was accomplished using the independent t-test. And the non-normally distributed data were subjected to the Mann-Whitney test. Furthermore, the Chi-square and Fisher's exact tests were used to compare the qualitative variables between the two groups. The relationship between the grading qualitative and quantitative variables was also investigated using the Spearman correlation test. Furthermore, the Pearson correlation test was used to investigate the relationship between two quantitative variables when at least one of them had a normal distribution.

A p-value of ≤ 0.05 was considered statistically significant in all calculations. The minimum sample size was estimated as 25 cases in each group considering α of 0.05 and β of 0.1 using the PASS software.

3- RESULTS

This study involved the investigation of 30 permanent congenital hypothyroid children and 32 healthy controls selected from the patients' family members. The two groups were comparable in terms of birth weight, length, and head circumference, current weight and height, age, and gender (**Table 1**).

Based on the results, healthy children had significantly higher total, verbal, and performance IQ, compared to those with permanent congenital hypothyroidism. This difference was higher in terms of verbal and total IQ but lower with regard to performance IQ (**Table 2**).

Among the affected children evaluated, information related to the age at the onset of treatment and primary TSH levels was available in 17 cases. These data and those regarding the frequency of TSH are presented in **Table 3**. The relationship between the age at the onset of treatment, primary TSH, and frequency of TSH elevation with verbal, performance, and total IQ was also evaluated (**Table 4**). According to the results, the age at the onset of treatment had a significant relationship with verbal IQ (r=-0.521; P=0.032). In this regard, earlier treatment was associated with higher verbal IQ. However, this variable showed no significant correlation with performance and total IQ scores. Furthermore, the results revealed no statistically significant relationship between primary TSH level and verbal and total IQ scores. Nonetheless, the primary TSH level was correlated with performance IQ score (r=-0.559; P=0.020). In this regard, lower primary TSH was associated with higher performance IQ. Additionally, the frequency of TSH elevation demonstrated no significant relationship with verbal, performance, and total IQ scores.

Table-1: Demographic variables in case and control groups

Variables		CH cases	Control group	P-value
Gender (female/male)	Number (%)	13(43.3) /17(56.7)	14(43.8) / 18(56.2)	0.974
Age (year)	Mean ± SD	9.60 ± 2.17	9.50 ± 2.09	0.854
Birth weight (g)	Mean ± SD	3216 ± 495	3378 ± 399	0.162
Birth length (cm)	Mean ± SD	49.50 ± 1.96	50.30 ± 1.20	0.062
Birth head circumference (cm)	Mean ± SD	35.22 ± 1.21	35.37 ± 0.92	0.613
Current weight (kg)	Mean ± SD	30.73 ± 9.49	32.53 ± 8.47	0.43
Current height (cm)	Mean ± SD	132.40 ± 14.2	135.70 ± 12.80	0.338

CH: Congenital Hyperthyroidism, SD: Standard Deviation

Table-2: Verbal, performance and total IQ in case and control groups, n= 62

Variables		CH cases	Control group	P-value
Verbal IQ	Mean ± SD	104.53 ± 13.30 (74-126)	121.34 ± 16.74 (96-155)	<0.001
Performance IQ	Mean ± SD	93.13 ± 7.42 (80-109)	99.65 ± 11.92 (80-133)	0.013
Total IQ	Mean ± SD	98.03 ± 7.94 (82-110)	110.78 ± 14.15 (90-148)	<0.001

CH: Congenital hyperthyroidism, IQ: Intelligence Quotient

Table-3: Descriptive statistics of congenital hyperthyroidism cases based on the onset of treatment, primary thyroid-stimulating hormone, and frequency of thyroid-stimulating hormone elevation

Variables	Maximum	Minimum	Mean/ Median
Age at onset of treatment (day)	27.35± 7.27	16	40
Primary TSH (mU/L)	30	8	>100
Frequency of TSH elevation	3	0	7

TSH: Thyroid-Stimulating Hormone

Table-4: Verbal, performance, and total IQ in correlation to the age at the onset of treatment, primary thyroid-stimulating hormone, and frequency of thyroid stimulating-hormone elevation

Variables		Verbal IQ	Performance IQ	Total IQ
Age at onset of treatment	Pearson Correlation P-Value	-0.521 0.032	0.029 0.913	-0.448 0.071
Primary TSH	Pearson Correlation P-Value	0.103 0.694	-0.559 0.020	-0.194 0.457
Frequency of TSH elevation	Pearson Correlation P-Value	0.40 0.835	0.02 0.884	0.104 0.584

TSH: Thyroid-Stimulating Hormone, IQ: Intelligence Quotient

Thyroid imaging results were evaluated in 27 patients, out of whom 11 (40.7%) cases had normal imaging findings (dyshormonogenesis), while 1 (3.7%), 5 (18.5%), and 10 (37%) patients suffered from agenesis, ectopic thyroid, and hypoplastic thyroid, respectively. The progression of height and weight growth was found to be appropriate in all children in both groups. Among the congenital hyperthyroid cases, two individuals developed almost out of the normal range. In this regard, one case started walking at about 18 months of age, and the other one started talking at the age of nearly 18 months, which could not be considered a developmental delay. The other children in both congenital hyperthyroid and healthy groups had a normal development with no significant difference between the two groups (P=0.230).

4- DISCUSSION

This study was focused on the evaluation and comparison of IQ in permanent congenital hypothyroid children and their healthy family members. Our results demonstrated that although the mean IQ of the congenital hypothyroid cases was within a normal range, all verbal, performance, and total IQ scores were significantly higher in the healthy control group, as compared to those in the permanent congenital hypothyroid group. In addition, our study showed an association between earlier treatment and higher verbal IQ, as well as between lower primary TSH and higher performance IQ. Furthermore, neither verbal, performance, nor total IQ scores showed a relationship with the frequency of TSH elevation.

In the current study, the mean IQ of the congenital hyperthyroid cases was within the normal range but lower than that of the control group. Our results are consistent with those reported in many other studies (12, 14, 19-22). In a study performed by Dimitropoulos et al., the difference between the total IQ scores of case and control groups was estimated as 9.7, while it was 12.7 in our study (19). However, some studies have reported evidence on IQ deficits despite the implementation of early treatments (19, 23-25). Our findings indicated that the age at the onset of treatment and primary TSH level affected the final IQ score. In the present study, earlier treatment was associated with higher verbal IQ scores. Furthermore, a lower primary TSH level was found to be correlated with a higher performance IQ.

Similar to our results, in another study conducted by Najmi et al. in Isfahan, Iran, the mean IQ was lower in both permanent and transient chronic hyperthyroid patients than in normal children. Furthermore, this mean was reported to negatively correlate with primary TSH and the onset of treatment (20). In addition, in a study carried out in France, treatment time (<day 21) was identified to be a more important

factor for IQ score. However, in another study, the severity of congenital hypothyroidism, rather than the time of treatment initiation, was correlated with IQ and motor score (26). Nonetheless, this association was not observed in some studies (19, 27, 28). In line with our findings, the results of a study conducted in Guilan, Iran, demonstrated that the patients identified in the neonatal screening program and subjected to early treatment had normal growth similar to the general population (29).

The evaluation of a screening program in Mashhad for the first time was an important strength of this study. In this research, the effect of confounding factors was highly restricted by individually matching the congenital hyperthyroid cases with healthy children based on age, gender, genetic factor. One of the main limitations of the study was the lack of access to all the required basic information due to the incompleteness of patient records and maternal information incompetence.

5- CONCLUSION

The mean verbal, performance, and total IQ in the treated patients were within the normal range, indicating a relative success of the plan. However, the mean values were significantly lower in the congenital hyperthyroid patients than in the healthy children. The present study provided valuable information on the success rate of the screening program in Mashhad. This highlights the importance of identifying and managing patients as early as possible and continuing follow-ups and proper parental education.

6- CONFLICT OF INTEREST

There was no conflict of interest.

7- ACKNOWLEDGMENT

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