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Comparison of Developmental Status between Early Treated Congenital Hypothyroid and Healthy Control Children

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ABSTRACT

Background: Early diagnosis and treatment of congenital hypothyroidism is the primary goal of neonates and children screening programs. This study aimed to evaluate and compare developmental skills in children with early-treated congenital hypothyroidism with healthy children using the Ages and Stages Questionnaires test (ASQ).

Methods: A total of 40 neonates with congenital hypothyroidism diagnosed during neonatal screening (thyroid stimulating hormone (TSH) > 10 mu/l) who were treated with Levothyroxine (10-15µ/kg) promptly within the first month of birth (after treatment, TSH < 4 mu/l) were evaluated for developmental skills using the ASQ test at 4, 8, and 12 months of age. The control group consisted of 40 healthy children matched with the case group in terms of age, sex, and socio-economic status. Chi-square and Fisher exact test were used with SPSS statistical software version 21 for analyzing the results.

Results: The overall mean ASQ score in case group was 262.7 ± 9.07 , and in control group was 261.2 ± 8.49 , which indicates no significant difference ($P > 0.05$). The ASQ test score increased significantly by age ($P < 0.05$). The girls' mean score of the ASQ test was significantly higher than boys in the case group ($P < 0.05$). Moreover, no significant difference was observed between the mean ASQ test score and the delivery type ($P < 0.05$).

Conclusion: This study showed that the developmental skills in children under-treatment of congenital hypothyroidism were at the standard level, indicating the effectiveness of early treatment to avoid developmental disorders.

Introduction

Congenital hypothyroidism is the most common cause of preventable and treatable developmental disorder in infants and children, leading to mental retardation and developmental disorders if not treated early. Thyroid hormones are fundamental for growth, maturation, and organogenesis of the central nervous system and suitable development depends on it for the critical time between fetal life and two years of age. Despite diagnostic screening and early treatment of neonates with congenital hypothyroidism, there are reports of a noticeable prevalence of neurodevelopmental disorders in the cognitive contexts of language learning, speech, and cognitive impairments in hypothyroidism cases.¹⁻¹¹

The disease prognosis can significantly improve by screening for congenital hypothyroidism in children. Prior to the introduction of neonatal screening programs; the diagnosis of hypothyroidism was delayed, resulting in severely reduced developmental skills and disorders. In Iran, the congenital hypothyroid screening program was integrated into the health system in 2005 by taking blood samples from the heel on the 3rd-5th day of birth and checking TSH level.¹²

There is a controversy about the prognosis of patients with congenital hypothyroidism under treatment. Some studies have shown that neurological symptoms and mental and developmental disorders are evident despite the start of treatment in 10% of patients.^{7,12,13} Therefore, there is disagreement about whether the treated patients have normal motor and cognitive skills. Due to the importance of this issue and the limited number of studies that have examined the developmental status of treated hypothyroid children, this study aimed to evaluate the developmental status of infants with congenital hypothyroidism, diagnosed by neonatal screening, with a healthy control group of infants via the Persian version of the

four, 8, and 12 -months ASQ in Yazd, Iran.

Materials and Methods

The ethics committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran, has approved this study (IR.SSU.MEDICINE.REC.1399.308470). This study is a case-control study that was conducted in 2019-2020 in Yazd province.

In order to select the study population, neonates with congenital hypothyroidism (CH) were included. The names of the infants with a definitive diagnosis of congenital hypothyroidism were obtained from the Vice-Chancellor for Health of Shahid Sadoughi University of Medical Sciences in Yazd. The control group consisted of healthy infants matching with the case group in terms of gender, age, and socioeconomic status who had no history of perinatal or postnatal disease affecting the central nervous system.

According to the national congenital hypothyroidism screening protocol, thyroid-stimulating hormone (TSH) was measured by heel prick blood samples in neonates within 3-5 days of birth. Retesting was performed for infants with $TSH \geq 5$. Those with $TSH > 10$ μ U/l and $T4 < 6.5 \mu$ g/dL were identified as congenital hypothyroidism.

Neonates with a definite diagnosis of CH were promptly treated (Start of treatment not later than four weeks after birth or immediately after confirmatory (serum) thyroid function testing in neonates) with levothyroxine tablets at a dose of 10-15 μ g/kg/day.

Then, selected case and control infants were followed and were evaluated at four, eight, and 12 months of age by the Persian version of ASQ for developmental skills.

Inclusion criteria included gestational age > 37 W, Apgar score > 8 , birth weight between 2500-4000 g, No history of asphyxia at birth, No history of NICU admission, beginning of treatment during the first month of life in CH cases. Infants who did not have $T4 > 9 \mu$ g/dL within three weeks, and $TSH > 4 \mu$ U/l at 4-6 weeks of treatment and cases who did not have regular follow-up

during the first year of life were excluded from the study.

Each questionnaire contains 30 questions in five domains, and six questions were asked in each. The questions were arranged from easy to difficult. The scores of the questions related to each developmental domain were added together, and then the child's developmental status was evaluated based on a comparison of the overall score. Also, each studied individual was categorized into normal and abnormal groups using the cut points.

If the average score obtained in each developmental domain is less than the cut-off points, it was considered as a delayed development in that particular domain. In each developmental domain, 60 points were the maximum score that can be obtained, and for each question, the maximum score that can be acquired is 10.

Statistical analysis: The sample size was calculated based on Z formula with an error of 0.05, a confidence interval of 95%, and a test power of 0.80, indicating 40 samples for each study group.

The data were analyzed using SPSS statistical software version 21 (IBM Corp., TX., US.). Chi-square test or Fisher exact test were used for data analysis of qualitative variables and the mean values in two groups, and more than two groups were compared using independent T-test and ANOVA (analysis of variance) test, respectively. Differences in P values less than 0.05 were considered significant.

Results

In this study of 40 children in each group, 25 (62.5%) children in control group and 23 (57.5%) children in cases group were females ($P = 0.91$).

According to the developmental domains evaluation results comparing cases and control groups, only in the second domain cases have a significantly higher mean score ($P < 0.05$). However, there were no significant differences between the mean of other developmental domains in the patient

and healthy groups ($P > 0.05$) (Table 1).

Table1. Comparison of the ASQ's Overall Mean Score in Any Developmental Domain in Two Groups

Domains	Cases group	Control group	P
Communication	51.61 ± 4.09	52.55 ± 3.7	0.10
Gross motor	53.27 ± 3.8	51.94 ± 3.9	0.02
Fine motor	52.94 ± 3.8	53.88 ± 3.8	0.1
Problem solving	52.22 ± 4.3	51.27 ± 4.2	0.14
Personal-social	52.7 ± 4.1	51.6 ± 4.09	0.07
Overall	261.2 ± 8.49	262 ± 9.07	0.25

The ASQ's overall mean score in patients was 262.7 ± 9.07 and in healthy individuals was 261.2 ± 8.49 , which indicates no significant difference ($P > 0.05$) (Table 1).

Table 2 compares the mean total score of the ASQ test regarding demographic variables in healthy and sick groups. Based on the results, with increasing age in case and control groups, the ASQ test score increased significantly ($P < 0.05$). The mean score of the ASQ test in the girls' was significantly higher than boys in the patient group ($P < 0.05$).

Furthermore, no significant difference was seen between the mean ASQ test score and the delivery type ($P > 0.05$). Sub-domain analysis demonstrated that the mean score of the ASQ test in communication in the patient group at four months is significantly higher than healthy ($P < 0.05$). In other ages in this domain, there was no significant difference between healthy and case subjects. In the gross motor domain, the ASQ test's mean score in the case group at eight months of age was significantly lower than healthy infants ($P < 0.05$). In other ages, there was no significant difference between two groups.

Comparing the ASQ test's mean score in the fine motor and problem-solving domains regarding demographic variables in the case and control groups revealed no significant difference between them.

In the ASQ test's personal-social domain regarding demographic variables, the mean score of the ASQ test in the patient group in boys was significantly lower than healthy infants in the same group ($P < 0.05$).

Table 2. Comparison of the Mean Total Score of ASQ Test Based on Demographic Variables in Two Groups

Variable		Cases group	Control group	P
Age	4 months	257 ± 7.03	256.66 ± 5.6	0.68
	8 months	260.5 ± 5.14	265.5 ± 10.61	0.02
	12 months	266 ± 10.28	266.16 ± 6.9	0.94
Overtime P		0.001	0.001	N/A
Gender	Female	262.89 ± 9.3	264.16 ± 8.58	0.47
	Male	258.48 ± 5.7	261.16 ± 9.35	0.15
Overtime P		0.007	0.12	N/A

In other cases, there was no significant difference between healthy and sick infants.

Table 3 compares the total ASQ test results in terms of demographic variables in case and control groups. According to the table results, in both groups, abnormal developmental status decreased significantly with age. Also, developmental delay was observed significantly higher in boys than girls in the case group.

Discussion

Congenital hypothyroidism in children is one of the most common congenital diseases that can lead to mental retardation, growth retardation, and delayed neuromotor development.^{1,2,5,7,8}

According to the results, developmental indices in children with congenital hypothyroidism who were treated are not significantly different from healthy children. The mean overall score of the ASQ test increased significantly with age. Also, the average total score of the ASQ test was higher in females than males.

A study conducted by Soliman et al. examined the incidence of developmental

disorders in 30 children with congenital hypothyroidism under treatment. It was shown that the incidence of developmental disorders in the communication domain in children with congenital hypothyroidism was not significantly different from healthy children.¹⁴ In a historical cohort study, Mozafari Kermani et al. evaluated 122 infants with congenital hypothyroidism under treatment and 122 healthy children between one and three years of age using the ASQ questionnaire for developmental disorders. Based on this study, no significant difference was observed in the ASQ test score in both groups.¹⁵ These findings were consistent with the present study results. However, the present study results were contrary to Frezzato et al. study.¹¹ In their study, fetal and neonatal hypothyroidism had different effects on the development of different parts of the brain during the first two years of life, such as impaired postural control associated with fetal hypothyroidism and speech problems and communication problems have been linked to the severity of hypothyroidism after birth.¹¹

Table 3. Frequency of Developmental Delay in Any Developmental Domain Based on Demographic Variables in Both Groups

Variable		Cases group		Control group	
		Normal (%)	Abnormal (%)	Normal (%)	Abnormal (%)
Age	4 months	28 (70)	12 (30)	31 (77.5)	9 (22.5)
	8 months	37 (92.5)	3 (7.5)	37 (92.5)	3 (7.5)
	12 months	39 (97.5)	1 (2.5)	40 (100)	0
P		0.05		0.001	
Gender	Female	62 (89.9)	7 (10.1)	69 (92)	6 (8)
	Male	42 (82.4)	9 (17.6)	39 (86.7)	6 (13.3)
P		0.02		0.5	
Delivery	Normal	50 (92.6)	4 (7.4)	46 (90.2)	5 (9.8)
	C-section	54 (81.8)	12 (18.2)	62 (89.9)	7 (10.1)
P		0.23		0.37	

Another similar study has shown that children with congenital hypothyroidism are at higher risk for motor and cognitive disorders.¹⁶ It was suggested that motor and mental development is normal in most children with hypothyroidism if the disorder is diagnosed without delay and treatment is started immediately in the first two weeks after birth.¹⁷⁻²⁰ These results are consistent with the present study's findings. According to the study results, the average overall score of patients' developmental status assessment in girls was significantly higher than in boys. Also, according to cut-off points analysis, the abnormal values for males were significantly higher than abnormal values of females. In most studies, the incidence of developmental disorders has been reported more in girls. In studies conducted in Saudi Arabia, Estonia, and China, the incidence of developmental disorders in girls has been reported more than in boys.^{21,22} However, in a Yazd province study, there was no significant difference between females and males. This difference can be attributed to the small sample size and the study's short duration.²³

A study conducted by Razavi et al. examined children's development with congenital hypothyroidism treated using the ASQ test. It was shown that the ASQ test score in 41% of children with congenital hypothyroidism under-treatment was abnormal. Also, the highest frequency of developmental disorders has been observed in girls, which is consistent with the present study results. The considerable difference between the above study and our study was that the children were monitored for three years and were able to compare both persistent and transient types.²⁴

Based on the present study results, no significant relationship was observed between the type of delivery and abnormal neurodevelopment in children in both groups. This result was approved by additional cut-off point analysis. Molkenboer et al. found no significant difference between the ASQ scores of neonates who had a cesarean section or a

normal delivery. Also, in those born with normal vaginal delivery due to breech position and weighing more than 3500 grams, the neurodevelopmental disorder was more prevalent.²⁵ These findings are consistent with our study results, indicating no statistically significant relationship between the type of delivery and developmental disorders in different areas.

Conclusion

According to the study, children's developmental skills in congenital hypothyroidism cases treated promptly were normal and not significantly different from healthy children. Therefore, newborns diagnosed with congenital hypothyroidism in a national screening program should be treated promptly, visited at regular intervals, and monitored for neurodevelopment.

Conflict of Interests

Authors have no conflict of interests.

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