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Neurodevelopmental Outcome of Preterm Infants with Hypothyroidism

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Abstract

Background: Hypothyroidism is one of the most common causes of preventable intellectual disability and is common in preterm infants. Some studies have reported that developmental delay is still high in these patients despite appropriate treatment.
Objectives: This study aimed to investigate the short-term neurodevelopmental outcome of preterm infants with thyroid dysfunction.
Methods: This cohort study included 50 preterm infants with thyroid dysfunction requiring levothyroxine treatment (case group) and 50 age- and sex-matched healthy preterm infants with normal thyroid tests (control group). The patients were followed, and Ages and Stages Questionnaires (ASQ) (including five domains) were filled out at 6 and 12 months to evaluate the short-term neurodevelopmental outcome.
Results: There was no statistically significant difference in gestational age, sex, and birth weight between the two groups (P-values = 0.648, 0.756, and 0.866, respectively). A total number of 4 (8%) and 7 (14%) of the case group and 1 (2.85%) and 2 (5.71%) of the control group had a possible neurodevelopmental delay based on the low score in at least one domain of ASQ at 6 and 12 months of age (P-values = 0.321 and 0.222, respectively). Treated hypothyroidism was not significantly associated with higher impaired neurodevelopmental outcomes (P-value = 0.236, Odd Ratio: 2.686, 95% CI: 0.523 - 13.787).
Conclusions: In this study, the risk of neurodevelopmental impairment in preterm infants with hypothyroidism was similar to that of healthy preterm infants. Thus, these findings may confirm the adequacy of levothyroxine replacement therapy in preventing neurodevelopmental delay.

Keywords: Ages & Stages Questionnaire (ASQ), Neurodevelopment, Preterm Infants, Thyroid Dysfunction, Hypothyroidism

1. Background

The prevalence of postnatal thyroid dysfunction has increased during the recent two decades, possibly due to better diagnosis through hypothyroidism screening programs and increased survival of premature infants (1-3). Hypothyroxinemia is common in preterm infants, occurring in 20% of preterm infants born before 34 gestational weeks and 29% of infants with gestational age under 32 weeks (4-6). A study in Wisconsin reported a congenital hypothyroidism prevalence of 1.56% among infants with gestational age less than 32 weeks and birth weight less than 1500 gr (7).

Hypothyroidism causes the imperfect maturation of neuronal and glial cells. It reduces synaptic densities and myelin during critical periods of development and consequently can lead to major irreversible neural defects upon lack of appropriate treatment. Thus, early screening and treatment of hypothyroidism in preterm neonates is paramount to (8, 9). However, there are some concerns that despite early and adequate treatment of these infants with thyroid hormone replacement, they may suffer from neurodevelopmental impairments such as reduced intelligence quotient (IQ), behavior and attention problems, and mild impairments in fine motor, communication, and visuospatial functions (10-15).

Correspondingly, Uchiyama et al. failed to detect any significant difference in the incidence of developmental delay between the treated and untreated VLBW infants with subclinical hypothyroidism, suggesting some unavoidable effects of prenatal hypothyroidism (14). On the other hand, administration of levothyroxine for infants under 27 weeks of gestational age was reported to be associated with improved psychomotor and neurological outcomes compared to the placebo group of the same gestational age (16).

2. Objectives

This study aimed to assess the short-term neurodevelopmental outcome of premature infants diagnosed with thyroid dysfunction during the neonatal period and treated with levothyroxine.

3. Methods

This case-control study received an ethics approval code (IR.TBZMED.REC.1398.012) from the Tabriz University of Medical Science ethics committee. Written informed consent was obtained from parents or guardians of infants.

This cohort study included premature infants (of gestational age $\leq$ 34 weeks) with thyroid dysfunction and treated with thyroid hormone that was born between March 2019 and February 2020 in the Al Zahra Hospital. Enrolled premature infants were treated with levothyroxine at an appropriate dosage (keeping thyroid-stimulating hormone [TSH] between 5 mU/L and 0.5 mU/L) and monitored by a pediatric endocrinologist. In the congenital hypothyroidism screening program in Iran, heel-prick samples of infants are collected third to fifth days after birth and measured for TSH levels. In premature infants, repeat samples are collected at 2, 6, and 10 weeks of life. Premature infants with more than 5 mU/L TSH levels in the second heal-prick sample undergo venous TSH and total thyroxine (T4) level measurements. The neonates detected to have hypothyroidism (TSH higher than 10 mU/L or low T4 values [less than 65 μg/L]) are referred to a pediatric endocrinologist for treatment (17), even if the results of the initial screening were normal. Serum TSH and T4 levels were measured at 35 and 55 days of life in all preterm infants born before 34 gestational weeks.

Using G-Power software and the results of the study of Ghazi et al. (18), m1 = 223.80 (Total development mean score) and with a default reduction of 5% in preterm infants with hypothyroidism (m2 = 212.6), sd1 = sd2 = 22, one-sided α = 0.05, power = 80%, the sample size was calculated as 49 infants in each group. In this study, 50 infants in each group were studied.

The control group was randomly selected from age and sex-matched premature infants with normal thyroid tests born at Al Zahra Hospital in the same period.

The exclusion criteria for both groups included infants with neonatal seizures, meningitis, hypoglycemia, inborn errors of metabolism, significant congenital defects or syndromes, birth asphyxia, and intra-ventricular hemorrhage grade II or more. A nurse who was blind to the patient's group and study purpose recorded the demographic profile of the neonates. Electrochemiluminescence immunoassays measured serum TSH and T4 using Roche Elecsus and Modular Analytics analyzers (Roche). The intra- and inter-assay coefficients of variation were 8.6% and 8.7% for TSH and 1.6% and 3.5% for T4, respectively (8).

Parents or guardians of infants fill out the Ages and Stages Questionnaire (ASQ) at the ages of 6 and 12 months after explanations of the items of the questionnaire.

Nineteen age-adjusted ASQ versions are available from 4 to 60 months. Each questionnaire consists of 30 questions and investigates five domains, including communication, gross motor, fine motor, problem-solving, and personal-social domains, with six questions in each category resulting in a domain-specific score. Parents or guardians are invited to answer these questions about the presence of specific skills and behaviors in their kids. The obtained scores are then compared to the expected mean score from a reference distribution of scores within age groups and categorized as: (1) Normal (above the mean), (2) in need of monitoring (1 - 2 standard deviations (SD) from the mean), (3) possible neurodevelopmental delay (> 2 standard deviations from the mean). The validity (0.86 to 0.91) and reliability (interrater > 0.85, test-retest > 0.90) of the system were ascertained by the Centre on Human Development (19, 20). Vameghi et al. provided the validated and standardized form of the Persian version of ASQ. They evaluated the reliability of the test among the 11000 participants aged 4 - 60 months old by Cronbach's alpha, which ranged from 0.76 to 0.86, and the inter-rater reliability was 0.93. The validity acquired by factor analysis was sufficient for (21). The present study used the Persian version of the ASQ with Iranian norms. In this study, the reliability of the ASQ was confirmed by determining internal consistency, and Cronbach's alpha was 0.87.

Patients with ASQ scores less than two standard deviations from the standard plot are considered to have a developmental impairment. Patients with a score ranging between 1 and 2 SD below the standard value were invited

to complete the questionnaire again 2 months later. Patients who had a possibility of a neurodevelopmental disorder were referred to pediatric neurologists to receive appropriate treatment and training.

All statistical analyses were performed using SPSS version (22). Frequency and percentage for qualitative variables and mean ± SD (standard deviation) for quantitative variables were reported. Comparisons between the two groups were conducted using unpaired Student's *t*-tests for continuous data and the chi-square test for categorical data. Results were considered statistically significant if P-values were less than 0.05.

4. Results

One hundred preterm infants with a mean gestational age of 30.16 ± 2.31 weeks were included, of which 49 patients (49%) were boys and 51 (51%) were girls. Fifty patients (50%) had thyroid dysfunction (case group), and 50 patients (50%) had normal thyroid tests (control group). The baseline characteristics of patients included in the two groups are shown in Table 1. The mean gestational age among newborns with thyroid dysfunction was 29.93 ± 2.16 weeks, and the gestational age at delivery in the control group was 30.68 ± 2.13 weeks (P-value = 0.648). The mean birth weight in neonates was 1335 ± 429 gr, which in the case group was 1283 ± 422 gr, and in the control group was 1436 ± 375 gr. There was no statistically significant difference in birth weight between the two groups (P-values = 0.866). In the case group, the mean TSH was 9.12 ± 0.37 mU/L, and the mean T4 was 58.87 ± 4.53 μg/L, and they started treatment at an average age of 37 ± 11.39 days old with levothyroxine at a dose of 12.5 mg daily for 7.68 ± 3.12 months.

The obtained ASQ scores in both groups are demonstrated in Table 2. Although the obtained scores in 6 months were lower in the case group compared to the control group, the differences were not statistically significant for all domains except for the personal-social domain (mean difference, 3.35; 95%Confidece interval, 0.89 to 5.81; P-value, 0.008). Likewise, the obtained scores in 12 months were lower in the case group compared to the control group. However, the differences were statistically significant in none of the domains, with P-value > 0.05 (Table 2).

A total number of four (8%) and seven (14%) of the case group and one (2.85%) and two (5.71%) of the control group had a possibility of neurodevelopmental delay in at least 1 domain at 6 and 12 months of age. Correspondingly, the number of patients with the possibility of neurodevelopmental impairment in each one of the five domains, in both 6 months and 12 months, was higher in the case group, but this difference was not statistically significant, with P-value> 0.05 for all domains (Table 3).

5. Discussion

In this study, 8% of preterm infants with hypothyroidism at 6 months of age and 14% of them at 12 months of age had a possibility of neurodevelopmental delay based on low ASQ scores at least in one of the five domains, including communication, gross motor, fine motor, problem-solving, and personal-social. Preterm infants with normal thyroid tests had impaired ASQ scores at 6 and 12 months in 2.85% and 5.71% cases, respectively. Preterm infants are vulnerable to developing hypothyroxinemia due to a lack of maternal thyroid hormone supply during the third trimester (22). On the other hand, there is delayed TSH elevation in response to low thyroid hormone levels because of the undeveloped hypothalamic-pituitary-thyroid axis in preterm infants (23). Although the thyroid function reaches the full-term infant level at 4 - 6 weeks after birth, some preterm infants have greater and more persistent thyroid dysfunction, which may require levothyroxine treatment (6). Van Wassenaer and coworkers reported that low thyroid hormone levels were associated with poorer neurodevelopmental outcomes in preterm infants with gestational age under 30 weeks (24).

However, Tan et al. did not find an association between transient hypothyroxinemia of prematurity or transient thyroid abnormalities with adverse neurodevelopmental outcomes at 2 or 5 years (25). They postulated that thyroid status may be reflected in the severity of illness or comorbidities such as intra-ventricular hemorrhage. In the study of Woo and coworkers, very low birth weight infants with a history of congenital hypothyroidism with delayed TSH elevation had similar growth and neurodevelopment at 18-month follow-up as compared with the control group (15).

In a study of 95 infants with treated hypothyroidism, developmental status was assessed by the Bayley test at 1 and 2 years of age. The results of this study demonstrated that the mean mental developmental index (MDI) of patients with hypothyroidism at 1 and 2 years of age was similar to the results of the normal population. Nevertheless, the MDI scores of the severe hypothyroid group at 2 years were significantly lower than the mean population (P <0.0001) (26). Another study on 42 children aged 24 to 36 months with a diagnosis of hypothyroidism and 40 healthy children as a control group, using the Bayley scale for infant development (BSID-II), showed no significant difference in terms of MDI and psychomotor

Table 1. The Baseline Characteristics of Included Patients in Two Groups [a]

Variables	All Neonates (N = 100)	Case Group (n = 50)	Control Group (n = 50)	P-Value
Gestational age (w)	30.16 ± 2.31	29.93 ± 2.16	30.68 ± 2.13	0.648
Gender				
Girl	51 (51)	24 (48)	27 (54)	0.756
Boy	49 (49)	26 (52)	23 (46)	
Birth Weight (gr)	1335 ± 429	1283 ± 422	1436 ± 375	0.866
TSH mU/L	9.12 ± 3.77	9.12 ± 0.37	4.12 ± 1.03	0.001
T4 μg/L	94.13 ± 28.93	58.87 ± 4.53	150.10 ± 10.47	0.001
Age of treatment initiation (day)	-	37 ± 11.39	-	
Duration of treatment (m)	-	7.68 ± 3.12	-	

[a] Values are presented as No. (%) or mean ± SD.

Table 2. Evaluation and Comparison of Infants' Performance in the Domains of Communication, Large Movements, Fine Movements, Problem-solving, and Socio-personal at the Age of 6 Months to 12 Months

Variables	All Neonates (N = 100)	Hypothyroidism (n = 50)	Control Group (n = 50)	P-Value	Mean Difference	95% CI of the Difference	
						Upper	Lower
Communication							
6 months	48.76 ± 0.79	47.60 ± 1.09	50.43 ± 1.09	0.079	2.82	5.99	- 0.33
12 months	48.12 ± 1.01	46.80 ± 1.49	50.00 ± 1.16	0.119	3.20	7.23	- 0.83
Gross motor							
6 months	43.94 ± 1.53	43.20 ± 2.03	45.00 ± 2.36	0.567	1.80	8.02	- 4.42
12 months	45.88 ± 1.34	45.10 ± 1.76	47.00 ± 2.10	0.490	1.90	7.35	- 3.55
Fine motor							
6 months	48.41 ± 0.76	47.30 ± 1.00	50.00 ± 1.14	0.082	2.70	5.74	- 0.34
12 months	48.71 ± 0.76	48.00 ± 1.03	49.71 ± 1.12	0.271	1.71	4.79	- 1.36
Problem-solving							
6 months	50.65 ± 0.53	49.90 ± 0.76	51.71 ± 0.68	0.095	1.81	3.95	- 0.32
12 months	51.41 ± 0.56	50.50 ± 0.81	52.71 ± 0.66	0.051	2.21	4.43	- 0.01
Personal-social							
6 months	49.88 ± 0.63	48.50 ± 0.87	51.86 ± 0.80	0.008	3.35	5.81	0.89
12 months	50.53 ± 0.73	49.70 ± 0.97	51.71 ± 1.08	0.176	2.01	4.94	- 0.91

developmental index (PDI) between these two groups (14). In a study conducted by Albert et al. on 44 patients with hypothyroidism and 53 healthy individuals as a control group with a mean age of 9 years, it was shown that the IQ and psychomotor development status of the case and control groups were comparable (10).

In contrast, Huo et al. compared the developmental quotient (DQ) index of 155 children with hypothyroidism at 24 months using the Gesell Development Scale (GDS) with 310 healthy controls. The mean DQ scores in hypothyroid patients were 7.5 points lower than adaptive behavior compared to the control group. Patients with severe hypothyroidism had the lowest DQ score compared to the other two subgroups (moderate and mild) and the control group (27). Also, Komur et al., using the Bayley III test, reported that cognitive, communication, and motor developmental scores were significantly lower in children with hypothyroidism than in controls (13). Therefore, some studies have emphasized the role of treatment initiation time. Thus, delayed initiation of treatment may reduce its effectiveness in preventing neurodevelopmental disorders in these patients.

Table 3. Prevalence of the Neurodevelopmental Disorder (Scores Less Than 2 Standard Deviations from the Standard Chart of ASQ) in Two Groups [a]

Variables	Delay In Hypothyroid Infants	Delay In the Control Group	P-Value
Communication			
6 months	2 (4)	0 (0)	0.087
12 months	4 (8)	0 (0)	0.231
Gross motor			
6 months	3 (6)	1 (2.85)	0.501
12 months	5 (10)	2 (5.71)	0.479
Fine motor			
6 months	1 (2)	0 (0)	0.400
12 months	3 (6)	1 (2.85)	0.501
Problem-solving			
6 months	2 (4)	0 (0)	0.231
12 months	2 (4)	0 (0)	0.231
Personal-social			
6 months	1 (2)	0 (0)	0.400
12 months	1 (2)	0 (0)	0.400
At least one domain			
6 months	4 (8)	1 (2.8)	0.321
12 months	7 (14)	2 (5.7)	0.222

[a] Values are presented as No. (%).

Furthermore, using different neurodevelopmental assessment tools with different accuracy may be another reason for differences among different studies. We have excluded infants with intra-ventricular hemorrhage that may impair neurodevelopment.

Our study had some limitations that should be regarded. The evaluation of the neurodevelopmental status of patients in the current study was conducted using ASQ, which is a self-reporting tool. Notably, ASQ is mainly used for screening and not the diagnosis of neurodevelopmental disorders. Therefore, we referred those who had a possibility of a neurodevelopmental disorder to pediatric neurologists to receive appropriate treatment and training.

In conclusion, the results of the current study showed that despite the low ASQ scores obtained by infants with thyroid dysfunction in all five domains, there was no statistically significant difference in the neurodevelopmental delay rate between the case and control groups at 12 months of age. These results may indicate that by means of appropriate and timely treatment of preterm infants with thyroid dysfunction, the risk of neurodevelopmental delay can be reduced, and these findings may confirm the adequacy of treatment of hypothyroid neonates in the prevention of neurodevelopmental disorders.

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Footnotes

Authors' Contribution: Rezazadeh. R. contributed to the conception of the work, conducting the study, and the acquisition, analysis, or interpretation of data for the work and revising the draft. Gharehbaghi. MM. contributed to the conception of the work, conducting the study, the acquisition, analysis, or interpretation of data for the work revising the draft, and approval of the final version of the manuscript. Ghergherechi. R. contributed to the conception of the work, drafting and revising the draft, and approval of the final version of the manuscript. Heidarabadi. S. contributed to the conception of the work, follow-up, drafting, and revising of the draft, and approval of the final version of the manuscript.

Conflict of Interests: The authors declare no conflict of interest.

Data Reproducibility: The data presented in this study are openly available in one of the repositories or will be available on request from the corresponding author by this journal representative at any time during submission or after publication. Otherwise, all consequences of possible withdrawal or future retraction will be with the corresponding author.

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