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Recovery Rate of Hyperthyrotropinemia and Its Associated Factors: A Prospective Observational Study

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ABSTRACT

Introduction: Hyperthyrotropinemia (HT) can be transient or permanent. There is no specific protocol in confirmatory tests to discriminate between transient and permanent forms. The aim of this study was to investigate the prevalence of transient HT and the factors that help to discriminate transient from permanent HT.

Methods: This was an observational prospective study in all neonates diagnosed with HT referred to the pediatric clinic of Boali Hospital, affiliated to Islamic Azad University Tehran Faculty of Medicine, Tehran, Iran during September 2017 and January 2019. The recovery rate was investigated during a three-month follow-up while withholding medical treatment. Data were analyzed with SPSS Version 22.0.

Results: Totally, 80 neonates (65% girls) were enrolled in this study. Among them, 62 participants (77.5%) recovered without any treatment during the three months of follow-up. The recovery rate was significantly higher in term newborns ($p < 0.01$). The mean weight of recovered neonates (2767.7 ± 440.2 gr) was significantly higher than that of the neonates who did not recover (2141.7 ± 755.2) ($p < 0.01$). The mean level of thyroid-stimulating hormone (TSH) of the recovered neonates (9.4 ± 3.0 mIU/L) was significantly lower than in the neonates who did not recover (22 ± 6.5 mIU/L) ($p < 0.01$).

Conclusion: The outcome of HT became mostly permanent in patients with a higher level of TSH. The prematurity and low birth weight were the influential factors on TSH level, which could indirectly increase the risk of HT permanence.

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Introduction

Congenital hypothyroidism (CH) is the most common congenital endocrine disorder in neonates. The thyroid hormone has a fundamental role in the growth and development of the brain. Hypothyroidism remains asymptomatic in many neonates. Therefore, a thyroid-screening test is carried out for all newborns during the first three to five days after birth, by measuring the thyroid-stimulating hormone (TSH) from the heel prick blood spot, to prevent the consequences of late diagnosis and treatment of CH. In the case of abnormal results of the primary screening test, a confirmatory test is requested (1, 2). Newborns who have an abnormal screening test and elevated TSH and normal T4 in the confirmatory test are considered hyperthyrotropinemia (HT).

HT has two types, namely transient and permanent. Transient HT is often resolved after a

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few weeks to a few months, but neonates with permanent HT will maintain the abnormal TSH level (3). A specific incidence rate for transient HT has not yet been determined, and various studies suggested an incidence range of 1 in every 8000 live births to 1 in every 17600 live births per year (4).

Different studies have suggested several causes for transient HT, such as prenatal iodine deficiency, prenatal iodine excess, maternal antithyroid medication, maternal hypothyroidism, and prematurity (5). Notably, 10% of neonatal hypothyroidism cases in the world are not detected despite the implementation of the thyroid screening protocol (6). Accordingly, a study recommended that hypothyroidism should be considered a potential cause in neonates with symptoms of developmental delay and prolonged jaundice (7).

Although a specific definition for transient HT has been proposed, there is no specific protocol in the confirmatory tests to discriminate between transient and permanent forms of HT in neonates (4). The management approach for these patients has been controversial. Some clinicians withhold treatment. Others treat the HT patients with thyroid hormone replacement for the first few years of life, and then gradually reduce the dose of levothyroxine (3, 8-10).

Although the latter approach can reduce the risk of side effects of neonatal hypothyroidism, it can increase the risk of overtreatment and complications for transient HT neonates (11). This study aimed to investigate the prevalence of transient HT, its associated factors, and the recovery rate without medical treatment to prevent the long-term potential side effects of this disorder, especially on brain development.

Methods

Study design

The present observational prospective study was conducted on neonates with HT referred to the pediatric clinic of Boali Hospital, affiliated to Islamic Azad University Tehran Faculty of Medicine, Tehran, Iran during September 2017 and January 2019. The recovery rate was investigated during a three-month follow-up, withholding medical treatment. The protocol of this study was approved by the ethics committee of Islamic Azad University Tehran Faculty of Medicine (Ethics code: IR.IAU.TMU.REC.1396.182). Written informed consent was obtained from the parents of all neonates before their participation in the study. All information was used privately and without mentioning the patients' names.

Study population

During this study, 2,556 neonates were referred to the vaccination section or pediatric clinic of Boali Hospital for the thyroid screening test. To measure the qualitative TSH level in these neonates, the heel prick blood spot was conducted in the first three to five days after birth. Those who had an abnormal screening test were referred to the laboratory department of Boali Hospital to measure the serum level of TSH and free T4 (FT4). All neonates with an abnormal screening thyroid test who had a TSH level between 6 and 60 mIU/L and normal FT4 (1.3 to 2.8 ng/dL) entered the study with the diagnosis of hyperthyrotropinemic hypothyroidism. The secondary assessment was done by measuring TSH at three months of age. During these three months, the neonates underwent a routine physical examination, every two weeks. The exclusion criteria were as follows: The primary TSH level of lower than 6 mIU/L or higher than 60 mIU/L, or the primary FT4 level lower than 1.3 ng/dL. Known cases of metabolic diseases and those whose parents did not give consent were also excluded from the study. Sampling was done with the convenience method, and all neonates who fulfilled our criteria entered the study.

Data gathering

In this study, the neonate's data including gender and maturity status (term, preterm), and history of jaundice (physiological, pathological, or none), congenital anomaly, and collagen vascular diseases were collected. Maternal data, including age and history of hypothyroidism, were also recorded. Weight measurement was done by a pediatrician using the same scaling instrument. The TSH and FT4 levels were assessed using the automated immune chemiluminescence assay kits (Abbott, IL, USA) in the laboratory of Boali Hospital. To investigate the recovery rate, the TSH level was measured again after three months of follow-up, and recovery was defined as a TSH level of 0.5 to 5.5 mIU/L.

Statistical analysis:

All data were analyzed with SPSS Version 22.0 (SPSS Inc., Chicago, IL, USA). Quantitative variables are described using mean ± standard deviation, and qualitative variables are presented using frequency and percentages. Chi-square test, one-way ANOVA, and independent sample T-test were applied to evaluate the difference between groups in terms of the target variables. A P-value < 0.05 was considered statistically significant.

Results

This study included 80 neonates with HT (65% girls). None of the neonates had a congenital

anomThis study included 80 neonates with HT (65% girls). None of the neonates had a congenital anomaly or collagen vascular disease. The descriptive information of the participants is shown in Table 1. Overall, 62 neonates (77.5%) recovered without any treatment during three months of follow-up.

The mean level of TSH in all neonates was 12.2 ± 6.6 mIU/L, and the TSH level was significantly higher in boys and preterm newborns ($p < 0.05$). The recovery rate was also significantly higher in term newborns ($p < 0.01$). Neonates with a history of maternal hypothyroidism had a lower level of TSH, but the difference (versus others) was not statistically significant ($p > 0.05$). Further, 60% of neonates had a history of physiological jaundice, and the level of TSH was higher among them, but the relation was not statistically significant ($p > 0.05$). The recovery rate did not have any significant relation with gender, maternal hypothyroidism, and history of jaundice ($p>0.05$).

The mean weight of the participants was 2626.8 ± 584.4 grams. The mean weight of the neonates who recovered (2767.7 ± 440.2 g) was significantly higher than that of the neonates who did not recover (2141.7 ± 755.2 g) ($p < 0.01$). There was also a significant relationship between the TSH level and birth weight ($p < 0.01$). Moreover, the mean age of mothers in participants was 26.9 ± 3.7 years, with a minimum and maximum of 12 and 35 years, and did not have any significant relation with the level of TSH and with the recovery rate ($p > 0.05$).

The mean level of TSH in neonates who recovered within three-month was 9.4 ± 3 mIU/L, and in neonates who did not recover was 22 ± 6.5 mIU/L. The relation between the recovery and TSH level was statistically significant ($p < 0.01$). Note that the recovery rate in neonates with a TSH level of lower than 10 mIU/L and in neonates with a TSH level of 10 to 20 mIU/L was 100% and 68.2%, respectively, while none of the neonates with a TSH level of more than 20 mIU/L recovered ($p < 0.01$).

Discussion

Hypothyroidism is very common in neonates. Many studies suggested different factors such as low birth weight or prematurity as the potential causes of changes in TSH level. Many cases of HT are transient who recover without any medical treatment. In this regard, the most important challenge is to discriminate between transient and permanent forms of HT and to manage it (2, 4,11).

In our study, 77.5% of neonates with HT recovered in a three-month follow-up without any medical treatment. In a study by Cody et al. in England, 2,735 neonates underwent a screening test. The serum level of TSH was then measured in 11 neonates with an abnormal screening test. They monitored 8 neonates for the HT outcome, and 4 of them recovered after 3 to 18 months (12). Kara et al. conducted a study on 130 neonates with an abnormal primary thyroid screening test, and the results showed that 16 (12%) had transient HT and recovered without any intervention (8). In another study, Calaciura et al. showed that the recovery rate among 56 infants with 16 to 44 months of age, who had an abnormal screening test and abnormal primary confirmatory test (elevated TSH and normal FT4), was 58% without receiving any treatment (13).

Some studies suggested the initial TSH level as one of the most important factors in the recovery

Table 1: Demographic and baseline information of studied neonates

Variable		Frequency (%)	Level of TSH Mean (SD)	P-value*
Gender	Boy	28 (35%)	14.6 (7.5)	0.02
	Girl	52 (65%)	11 (5.7)	
Maturity status	Term	64 (80%)	10.1 (4.5)	0.01
	Preterm	16 (20%)	21 (6.6)	
History of maternal hypothyroidism	Yes	17 (21.3%)	9.6 (4.6)	0.06
	No	63 (78.7%)	13 (6.9)	
Maternal iodine intake during pregnancy	Sufficient	48 (60%)	13.9 (7.3)	0.01
	Insufficient	32 (40%)	9.8 (4.5)	
History of jaundice	Physiological	48 (60%)	13.7 (7.3)	0.05
	Pathological	4 (5%)	8.6 (2.3)	
	None	28 (35%)	10.3 (5.1)	

TSH: Thyroid-Stimulating Hormone; SD: Standard Deviation. * P-value refers to the relation between each variable and the TSH level

of neonates with HT. Calacuira et al. mentioned that HT patients with a higher level of initial TSH were more likely to have the permanent form of HT, and the recovery rate was higher in those with a lower initial TSH level (13). In this regard, our study showed similarly that neonates with a lower initial TSH level had significantly a higher chance of recovery in the three month follow-up, as the mean TSH level in the recovered patients was 9.4 mIU/L and in the patients who did not recover was 22 mIU/L. However, contrary to our results, Unuvar et al. reported that 54% of infants with HT at three months of age were ended up with permanent CH after two to three years of follow-up. The initial TSH level was also similar in permanent and transient HT groups (4).

Our study showed that neonates with a lower birth weight had significantly higher initial TSH levels and a lower recovery rate. The recovery rate was also significantly lower in premature newborns. Tfayli et al. (14) investigated 104 preterm neonates with a very low birth weight in a retrospective study and indicated that patients with a late TSH rise had a significantly lower mean birth weight than those with an early TSH rise. Zung et al. (3) investigated 43 neonates with HT and showed that 35% of them were premature. Twenty one percent of neonates were small for gestational age (SGA).

Some nutritional factors such as sufficient iodine intake in pregnancy can affect the initial TSH level of neonates. Some studies suggested that iodine deficiency or surplus in pregnant women is associated with the initial TSH level of neonates. However, other studies found it ineffective (15-18). Nishiyama et al., in a study on 34 neonates with abnormal results of the initial screening test, showed that 15 neonates had a high level of urinary iodine. They explained it to be because of excessive iodine intake by mothers during pregnancy. The follow-up showed that 12 neonates ended up with permanent HT and required levothyroxine (15). In another study and among 236 pregnant women in Southern Thailand, Jaruratanasirikul et al. found the TSH level to be higher in neonates of mothers with less iodine intake during pregnancy, but the association was not statistically significant (19). Similar studies in Denmark and Austria did not find either any significant relation between low iodine intake in pregnant women and the TSH level in neonates (16, 17, 20, 21).

In our study, the initial TSH level was significantly higher in boys, but there was no significant association between gender and recovery rate. Studies assessed the role of gender in the initial level of TSH and recovery from a primary thyroid disorder. They indicated that the prevalence of transient thyroid disorder in boys was twice more than in girls (9). However, a study in the USA showed that this proportion was declining (22). In another study on neonates with HT, Unuvar et al. did not find any association between gender and the initial TSH level or recovery rate (4). Kara et al. also showed that all investigated factors were the same in both transient and permanent forms of HT, but the proportion of girls to boys was 0.6 in the transient form and 1.5 in the permanent form (8).

Hypothyroidism in mothers can lead to HT or CH in neonates due to the transmission of TSH blocking antibodies through the placenta (23). However, some studies showed contradictory results. Kvetny et al. (24) found that there was no significant difference in the thyroid status of neonates of mothers with or without autoimmune thyroid diseases. Similarly, Banakar et al. conducted a study on 30 neonates whose mothers had a thyroid disorder and showed that although some had an abnormal initial level of TSH but all had eventually a normal TSH level after two weeks (25). In this regard, our study showed no significant association between the maternal history of hypothyroidism and the TSH level or the recovery rate.

The thyroid function is evaluated in all neonates with prolonged jaundice. Unachak et al. discussed that prolonged jaundice was the most common clinical sign in 48 neonates with CH in the first three months after birth (26). Consistent with previous studies, our study showed that the initial TSH level was higher in neonates with physiologic jaundice, but the difference was not significant (27-29).

The small sample size and short study period were the limitations of this study. It is highly recommended to do further studies with a larger sample size with more variables such as the maternal serum and urine level of iodine, TSH level or iodine status during pregnancy, and socioeconomic status. Longer follow-up can also increase the accuracy of predicting recovery and outcome.

Conclusion

This study showed that the TSH level could be a useful predictive factor for the HT outcome. A higher level of TSH increased the risk of HT becoming permanent. Influential factors on TSH level, including prematurity and low birth weight, can indirectly increase the risk of permanent HT. Being aware of these factors can help to discriminate between the transient and permanent forms of HT and to reduce the side effects of missed diagnosis or overtreating.

Conflict of interest

The authors declare no conflicts of interest.

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