Thyroid Function Test in Pre-term Neonates During the First Five Weeks of Life

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ABSTRACT

Background: Congenital hypothyroidism (CHT) is one of the most common congenital endocrinal disorders. The prevalence of CHT is estimated about 1 in 3,000 newborns. The prevalence, etiology and associated disorders of abnormal thyroid screening tests are reported in different ranges. In this study, we assessed the pre-term newborns for CHT and associated factors that influence thyroid function.

Methods: One hundred newborns with the gestational age fewer than 35 weeks were investigated. Baseline serum thyroid stimulating hormone (TSH) and free thyroxin (FT4) levels were measured during the first 5 days of life and were repeated during the first 5 weeks. We analyzed the effects of demographic factors and the presence of respiratory distress syndrome on the alteration of thyroid function tests during the first 5 weeks of life.

Results: The mean gestational age (GA) at delivery was 32.35±1.97 (range 28 to 35) weeks. CHT was observed in 13(13%) preterm infants. GA was the only factor which affect the FT4 changes over the two weeks follow-up ($P < 0.001$, b*: -2.783, Power: 70.2%*) although the differences between baseline and follow-up amount of TSH were not significantly influenced by GA ($P = 0.062$, *power: 46%*). However, the adjusted TSH and FT4 serum level changes during follow-up were significantly different between two groups (between CHT and normal, $P = 0.006, 0.000$, respectively).

Conclusions: It seems that thyroid function tests should be repeated in preterm infants, especially for patients with lower gestational age, to confirm the diagnosis of CHT. Also, CHT should be considered among the newborns that are affected by RDS.

Keywords: Congenital hypothyroidism, pre-term neonate, respiratory distress syndrome, thyroid screening tests

Original Article

INTRODUCTION

Congenital hypothyroidism (CHT) is one of the most common endocrinal disorders and also the most common cause of treatable mental retardation. Prevalence of CHT is estimated about 1 per

3,000 newborns.[1] Many of the neonates with CTH have few or no clinical presentation of thyroid hormone insufficiency but they become symptomatic by weeks or months after birth, gradually.[2] Serum T4 concentrations of fetus umbilical cord who cannot release any thyroid hormone are about 25 to 50% of those of normal that is because of seeping some maternal T4 within the placenta.[3] Therefore, it is difficult to surmise newborns that are susceptible for CHT. There are some probable symptoms that may be present in newborns with CHT.[2-5]

Thyroid hormones are very important for differentiation and maturation of various tissues such as brain (the most of thyroid-dependent brain maturation occurs 2 to 3 years after birth) and bone (the bone age is often delayed at birth because of intrauterine hypothyroidism).[6] Therefore, it is expected to see premature organ in newborns with insufficient thyroid hormones. CHT can be sporadic (Approximately 85% of cases) or hereditary type (15%). Transient CHT (t-CHT) is a common condition which affected between 1:100 and 1:50,000.[6-9] The causes of t-CHT in newborn infants are iodine deficiency, anti-thyroid drugs given to mothers with hyperthyroidism, exposure of the fetus or newborn to high doses of iodine and maternal thyroid-stimulating hormone receptor antibodies.[9-11] CHT was firstly detected by a raised thyroid-stimulating hormone (TSH) level obtained between 3 to 6 days of age.[6]

Neonatal thyroid screening is necessary to make an early diagnosis of CHT and prompt thyroid replacement therapy under 1 month of age in the absence of suggestive symptoms. Neonatal thyroid screening in which either TSH or T4 (thyroxin) are measured in heel-stick blood specimens were extended in the mid-1970s to detect thyroid hormones insufficiency as soon as possible.[5,12]

The prevalence, etiology and associated factors of CHT and abnormal thyroid screening findings were reported different previously.[9,13,14] In this study, we assessed the preterm newborns for CHT and also we evaluated them for a possible relationship between CHT and clinical findings.

METHODS

In a concurrent cohort study, all of preterm newborns were consecutive followed that were born in Najmiyeh university Hospital, Tehran, Iran during 2009-2010. The inclusion criteria were including; preterm neonates (the gestational age 35 weeks and less), newborns who their parents have filled informed consent for investigation and the specimen were sufficiently gathered. Cases with positive maternal history of thyroid disorders (such as hypo or hyperthyroidism) or newborns of mothers who had used iodine-containing medications, neonates with obvious congenital disease or deteriorating conditions (such as sepsis) which can affect on thyroid status were excluded. Thyroid function tests (TFT) containing T4 and TSH were evaluated two times; first at days 3rd-5th after birth) and second at weeks 3rd-5th after birth).[15]The samples resource was included capillary blood species in amount of 2.5 ml at least and the specimens measured consecutively after taking them.

Gestational age (GA) was estimated by last menstrual periods and was confirmed by ultrasonography during the first trimester of pregnancy. Free T4 and TSH concentrations were measured by enzyme-linked-immunosorbent assay (Kit's name; Pishtaz Teb, Tehran, Iran). Transient CHT is defined as TSH level more than 10 micro Unit/mLit on 3-5th postnatal day with the FT4 level in normal ranges that TSH level was finally normalized in the follow-up period (3-5th postnatal week) without treatment and also the permanent CHT was defined as TSH level above 10 micro Unit/mLit and FT4 level under 10 pmol/Lit.[10,16]

TFT were repeated in all of the infants between the third and fifth week and no cases dropped out from the survey. Surfactant therapy (Survanta, U.S) would be administrated by a neonatologist, if the neonates had a severe respiratory distress. All infants and their mothers received no medications, which influence the thyroid function (lithium, amiodarone, hormonal medication) after discharge.

Clinical information containing gestational age (GA), birth weight (BW), the development of respiratory distress syndrome and requiring surfactant therapy were compared according to the first and second TFT findings. The RDS diagnosis was confirmed by a neonatologist and a radiologist consultant. Although, this study was a prospective cohort study, which was included all children with the inclusion criteria consecutively, the sample size was estimated with the statistician to be enough for multivariate analysis. This study and its informed maternal consent were approved by the research

Ethics Committee of the Baqiyatallah University of Medical Sciences, Tehran, Iran.

The data were analyzed using SPSS 17th edition (SPSS, Inc., Chicago, IL, USA) and were expressed as means ± standard deviations (SD) for quantitative data and percent for qualitative data. Analyses were accomplished by using the independent t-test (or the Mann-Whitney U test for non-parametric amounts) and the pearson chi^2 test (or fisher exact test) for categorical data. To evaluate the impact of the prenatal underlying factors on result of screening test, general linear model including repeated measurement ANOVA and logistic regression was used in two steps.

RESULTS

The mean GA at delivery for study group (100 neonates) was 32.35 ± 1.97 (range, 28-35) weeks, and the mean birth weight (BW) was 1650 ± 220 (range, 0.98-2.23) g. CHT was observed in 13 preterm infants (13%) that 11 of them were diagnosed as transient CHT by future evaluation. The mean (±SD) GA in neonates with normal TFT was 33.12 ± 2.01 months and the mean age in group with abnormal TFT was 32.07±3.14 months, this difference was statistically significant (P = 0.002). The difference between mean BW of groups with normal and abnormal TFT was not statistically significant (1150 ± 375 vs. 1368 ± 485 g, P = 0.131). The demographic characteristics in the two groups of cases (infants with CHT and normal) are presented in Table 1.

The mean of TSH was 3.65 ± 2.79 and 6.28 ± 3.00 micro Unit/mLit at the baseline and follow-up measurement, respectively and also the mean of FT4 was 10.55 ± 3.12 and 9.78 ± 1.98 pmol/Lit at the baseline and follow-up measurement, respectively. In univariated analysis, the differences between baseline and follow-up measurement of TSH and FT4 amounts were statistically significant (P = 0.003, 0.000, respectively). The TSH level changes during the follow-up periods were significantly different between two groups (infants with CHT and normal; P = 0.028) but this changes was not associated with GA, BW, gender, presence of RDS and receiving surfactant (P > 0.05). The FT4 level changes during the follow-up periods were significantly different between two groups (P < 0.001). Also, FT4 changes was significantly associated with GA (P = 0.003, r: –0.296) and presence of RDS (P = 0.045).

The incidence of respiratory distress syndrome (RDS) in preterm neonates with CHT was 30.8% and also the incidence of RDS in preterm neonates without CHT was 31.0% this difference in prevalence was not statistically significant (P = 0.629). By using the multinomial logistic regression model, we adjusted probable confounders such as GA and BW and we found that presence of RDS significantly associated with CHT (P: 0.000, β: 14.33)

In multivariate analysis by using the general linear model and linear regression, confounder variables were adjusted. Hence, we found that GA was the only factors which influenced the FT4 changes over the two weeks follow-up (P < 0.001, β: –2.783, *Power*: 70.2%). Furthermore, the differences between baseline and follow-up amounts of TSH were not associated with gestational age, significantly (P: 0.062, *Power*: 46%).[Chart 1] Moreover, the adjusted TSH and FT4 serum level changes during follow-up for GA were significantly different between two

Table 1: Demographic characteristics in both groups

Variable	CHT(N = 13)	Normal (N = 87)	*P*-value
Gestational age (weeks)	32.07 ± 3.14	33.12 ± 2.01	0.002
Male ratio	46.2%	44.8%	0.929
Weight (less than 3 Kg)	84.6%	63.2%	0.131
RDS	30.8%	31%	0.629 (adjusted <0.000)
Surfactant therapy	30.8%	33.3%	>0.05
First TSH	7.43 ± 2.83	3.08 ± 2.31	<0.000
First Free T4	7.68 ± 2.42	10.09 ± 1.70	<0.000
Second TSH	7.84 ± 4.23	6.05 ± 2.72	0.044
Second Free T4	4.03 ± 1.45	11.52 ± 1.87	0.004

CHT = Congenital hypothyroidism, Kg = Kilogram, RDS = Respiratory distress syndrome, *Bold is statistically significant adjusted for age, weight and gender

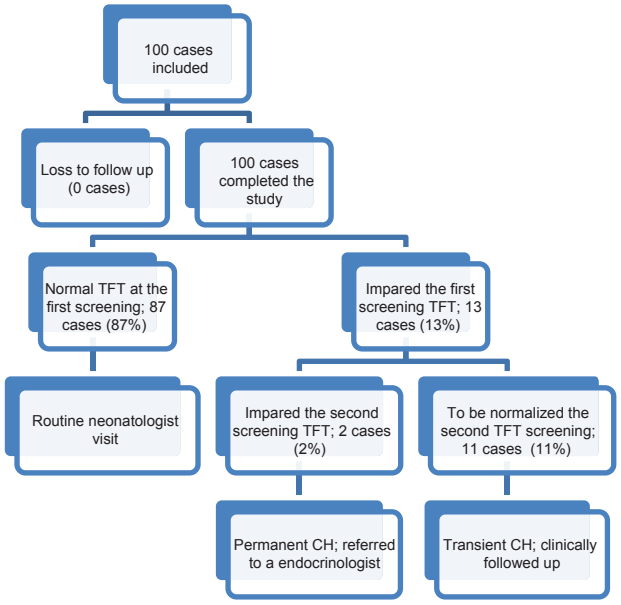

Chart 1: The plan of survey

groups (between CHT and normal, *P*: 0.006, 0.000, respectively).

DISCUSSION

In this study, the prevalence of CHT was observed 13% in preterm infants and 2% had permanent-CHT, which was higher than previous reports.[11] Iranian people are themselves susceptible for hypothyroidism.[17] We think that various socioeconomic factors may be included although there is no definite evidence. Also, the baseline amount of TSH and FT4 significantly changed during the follow-up period, which was not different with our knowledge. It seems that the FT4 depletion can induce TSH changes, although, these changes were influenced by GA. Van Wassenaer *et al*. conducted a prospective serial measurements of T4, FT4, T3, reverse T3, TSH, and T4-binding globulin (TBG) in 100 infants of <30 weeks of gestation, during the first 8 weeks of life and they found that FT4 level had decreased during the follow-up. Also, they concluded that the FT4 changes probably reflected a transient depletion of thyroidal hormone reservoirs.[18]

We found that GA was the only factor which could affect the TFT changes during the 2 weeks follow-up. Also, Van Wassenaer *et al*. revealed that the changes of FT4 mainly influenced by GA, which is concordant with our findings. In preterm newborns, RDS is a critical sickness over the few first week of life. There are some investigations on the determination of a possible relationship between this illness and serum thyroid hormone levels.[19] In addition, the pattern of TFT changes during the first month of age in preterm infants with medical problems, such as RDS or intrauterine growth retardation, might be different with normal newborns.[11,18] We found that presence of RDS significantly associated with CHT. Few studies demonstrated that preterm children with undercurrent illness (such as RDS) have a raise in amount of T4, FT4, T3, and TBG after birth, which is different with our findings.[11,18] In contrary, Simpson *et al*. declared that T3 and T4 were mainly regressed in neonates with severe illness and these changes was not associated with GA, which is different with our findings. They justified the relative maintenance of FT4 levels in their preterm newborns with decrease in binding of T4 to TBG when T4 levels are reduced, although it seems that it is a controversy because the TBG level changes along gestational age.[20]

In term newborns, serum T4 level decreases in the first week of life, especially in low birth weight preterm neonates. T4 clearance is more rapid in low birth weight and more preterm neonates than normal neonates.[21] In children from endemic areas of iodine deficiency (such as Iran), lack of iodine donates for the depletion of the serum level of T4. After the first week of life, serum T3 and T4 level progressively rise in most preterm newborns (those who were born at 23 to 27 weeks GA). The amount of thyroid hormones in preterm newborns fewer than 28 gestational ages, achieve to the normal range after 3 or 6 weeks of life.[18,22] Serum hormone assessments, consisting TSH and FT4 or T4 are necessary to confirm abnormal results of screening tests, therefore, we suggest one more screening evaluation after the 3rd-5th week of ages.[16] TSH is the key diagnostic test for CHT, although FT4 levels will be slightly different, depending on GA. The findings of screening test may be falsely positive in very low birth weight and preterm infants. It is possible to reduce potentially two thirds of false-positive results in very low birth weight and preterm infants with waiting until 24 to 48 h postnatal age to collect blood specimens.[23] Regarding to our results, TSH changes will not affected by GA, so standard ranges for term neonates can be used.[11,18,22,24]

More than 95% of newborns with CHT have few and even no clinical presentations of CHT at birth, but there was a high prevalence of morbidity among preterm neonates.[25] Regarding to the vital effect of thyroid hormones on nervous-system development, the screening and the treatment of patients with CHT is necessary. We suggest that for other aspects of additional disorders in patient with impaired TFT, more studies, especially a meth-analysis, should be performed. We suggest preterm neonates followed by the screening test for CHT at the first 5 weeks of age. Screening test and its follow-up should be performed between 2 and 4 weeks of age to distinguish the permanent CHT from transient form. Also, CHT should be considered among the newborns who affected by RDS.

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