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ARAŞTIRMA / RESEARCH

Relationship between thyroid function tests and small for gestational age in preterm newborns

Preterm yenidoğanlarda gebelik yaşına göre küçük olmak ile tiroid fonksiyon testleri arasındaki ilişki

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Abstract

Purpose: The aim of this study was to evaluate the relationship between thyroid hormone levels and clinical outcomes in preterm, small for gestational age (SGA) infants.

Materials and Methods: The premature newborns (gestational age of ≤30 weeks) were divided into two groups as SGA and non-SGA. Thyroid stimulating hormone (TSH) and free thyroxine (fT4) levels, the frequency of congenital hypothyroidism (CH), demographic and clinical characteristics, morbidity and mortality rate were compared between the groups.

Results: A total of 430 premature newborns, 72 in the SGA group and 358 in the non-SGA group were included. The frequency of CH, morbidity, demographic and clinical characteristics were similar between two groups. The mortality rate was higher in SGA (36.1%) than in non-SGA group (13.6%). Serum fT4 level was lower in SGA group (1.04±0.30 ng/dl) compared to the non-SGA group (1.24±0.33 ng/dl). The serum TSH level was higher in SGA group (9.91 ± 5.6 uIU/L) than in non-SGA group (6.6 ± 5.2 uIU/L).

Conclusion: The frequency of thyroid dysfunction was higher in preterm SGA infants compared to non-SGA, which was due to transiently high TSH and low fT4 concentrations. Therefore, thyroid function tests should be monitored periodically in preterm and SGA infants.

Keywords:. free thyroxine, infant, premature, small for gestational age, thyroid stimulating hormone

Öz

Amaç: Bu çalışmada erken doğmuş, gebelik yaşına göre küçük (SGA) bebeklerde tiroid hormon düzeyleri ile klinik sonuçlar arasındaki ilişkiyi değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Prematüre yenidoğanlar (gebelik yaşı ≤30 hafta) SGA olan ve olmayan olarak iki gruba ayrıldı. Gruplar arasında tiroid uyarıcı hormon (TSH) ve serbest tiroksin (sT4) düzeyleri, konjenital hipotiroidizm (KH) sıklığı, demografik ve klinik özellikler, morbidite ve mortalite oranları karşılaştırıldı.

Bulgular: SGA grubunda 72 ve SGA olmayan grupta 358 olmak üzere toplam 430 prematüre yenidoğan dahil edildi. KH sıklığı, morbidite, demografik ve klinik özellikler iki grup arasında benzerdi. Mortalite oranı SGA'da (%36,1) SGA olmayan gruptan (%13,6) daha yüksekti. Serum sT4 düzeyi SGA grubunda (1,04±0,30 ng/dl) SGA olmayan gruba göre (1,24±0,33 ng/dl) daha düşüktü. Serum TSH düzeyi SGA grubunda (9,91 ± 5,6 uIU/L), SGA olmayan gruptan (6,6 ± 5,2 uIU/L) daha yüksekti.

Sonuç: Tiroid disfonksiyonu sıklığı, geçici olarak yüksek TSH ve düşük fT4 konsantrasyonlarına bağlı olarak, preterm SGA bebeklerde SGA olmayanlara kıyasla daha yüksekti. Bu nedenle erken doğmuş ve SGA bebeklerde tiroid fonksiyon testleri periyodik olarak izlenmelidir.

Anahtar kelimeler: serbest tiroksin, bebek, prematüre, gebelik yaşına göre küçük bebek, tiroid uyarıcı hormone

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INTRODUCTION

Small for gestational age (SGA) baby refers to infants born with a birth weight <10th percentile for gestational week[1]. Every year, nearly 20% of infants are born as SGA infants[2]. Newborns with SGA have high morbidity in both the short and long term. They are at higher risk for impaired neurodevelopment and linear growth, as well as chronic medical conditions such as hyperlipidemia, endocrine problems, insulin resistance, obesity, and hypertension later in life[2-4].

After the routine use of the congenital hypothyroidism (CH) screening program in the neonatal period, L-thyroxine replacement therapy, which is started at 2 weeks of age, can normalize thyroxine (T4) and thyroid releasing hormone (TSH) levels and prevent developmental problems caused by late diagnosis[5]. CH is observed more frequently in premature infants than in term infants. In addition to the fact that neurodevelopmental problems are more common in a preterm infant compared to a term infant, the coexistence of prematurity and CH also increases the frequency of adverse clinical outcomes [6-10].

Since the hypothalamic-pituitary-thyroid axis maturation is insufficient in premature infants, temporary thyroid hormone imbalances are seen more frequently than in term infants[11]. It is thought that hypothalamic-pituitary-thyroid axis dysfunction may affect growth before and after birth[12]. A previous study suggested that TSH concentrations are significantly higher in premature SGA neonates, and that elevated TSH should be considered while determining a reference range for this population [13]. In addition to higher TSH concentrations in premature and SGA newborns, they are also more susceptible to thyroid dysfunction such as transient hypothyroidism and delayed TSH increase due to hypothalamic-pituitary thyroid axis immaturity [5].

Although SGA babies are known to be at risk for neurodevelopmental delay, SGA babies with thyroid dysfunction are thought to be at great risk for adverse outcomes in childhood as well. Thyroid dysfunction not only affects postnatal growth and neurodevelopment of SGA infants, but also reduces their intrauterine growth. However, there are not enough studies examining the effect of thyroid dysfunction in preterm infants with SGA. There are only a few publications on the early effects of thyroid hormones on morbidity and mortality in preterm infants with SGA. These studies conducted in countries other than Turkey, and provide valuable data on the effect of thyroid dysfunction in premature infants with SGA[1-3,5]. Furthermore, the incidence of thyroid dysfunction in premature infants with SGA in Turkey is not clearly known. According to the hypothesis of our study, thyroid function abnormalities can be seen in preterm infants with SGA in Turkey. Therefore, we aimed to investigate the frequency of CH and freeT4 (fT4) and TSH levels in preterm infants with SGA. Subsequently, our study aims to provide superiority in identifying preterm infants with SGA at risk for thyroid dysfunction. Thus, our findings will help both to follow these risky babies closely and to prevent negative outcomes in childhood.

MATERIALS AND METHODS

The study was conducted in Ankara City Hospital, Neonatal Intensive Care Unit (NICU) between March 1, 2021 – November 30, 2021. Premature babies whose gestational age was ≤ 30 weeks were included in the study. Newborns born at >30 weeks of gestation and with congenital anomalies were excluded from the study. The data of the patients were obtained retrospectively from the hospital medical records. The study was approved by the local ethics committee (Health Sciences University Zekai Tahir Burak Women's Health Education and Research Hospital ethics committee, ethic no: 102/2018, date: 18.12.2018). Informed consents were obtained from the parents for each newborn. All data collected during this study were kept confidential and not shared anywhere, in terms of the reliability of the records and the privacy of the patients included in the study. The authors acted in accordance with the Declaration of Helsinki while performing the study.

Procedure

Maternal age, maternal thyroid diseases, antenatal steroid administration, gestational week (GW), birth weight (BW), modes of delivery (normal vaginal route/cesarean section), Apgar scores (1st and 5th minutes), gender, fT4 and TSH levels, CH, early neonatal sepsis (ENS), late neonatal sepsis (LNS), respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), length of stay in the NICU and mortality were evaluated.

Sepsis in the first 72 hours after birth was defined as ENS, and sepsis after 72 hours was defined as LNS[14]. Preterm babies were evaluated with cranial ultrasonography every two days during the first week of life, and advanced stage (stage ≥3) IVC was recorded[15]. In clinical and echocardiographic evaluation, PDAs with hemodynamically significant ducts and requiring treatment were recorded[16]. Retinal examination was performed by an experienced ophthalmologist and patients with ROP requiring laser therapy were recorded[17]. If the corrected age of the preterm baby was 36 weeks or if the oxygen support is <30% at the time of discharge, it was defined as moderate BPD. If the oxygen requirement was ≥30% or if positive pressure ventilation support was present, it was defined as severe BPD. Moderate and severe BPDs were recorded[18]. Patients with surgical or severe NEC (stage >2) was recorded[19]. Patients who were given surfactant for respiratory distress were accepted as RDS[20]. A birth weight below the 10th percentile for gestational age was defined as SGA (symmetrical and asymmetrical)[4].

Examination of thyroid function tests

Serum fT4 and TSH levels were measured in all babies on the postnatal 5th day. Patients with serum TSH >20 uIU/L were accepted as CH and treatment was started. If serum TSH level was between 6-20 uIU/L and fT4 level was between 0.62-1.18 ng/dL, TSH and fT4 levels were measured again after 1 week. If the TSH was 6-20 uIU/L in the control, CH was accepted and treatment was started. If the first serum TSH level is between 6-20 uIU/L and fT4 <0.62 ng/dL, treatment for CH was started (22). Levothyroxine (8-12 mcg/kg/day) was started in patients with congenital hypothyroidism. The appropriate levothyroxine dose was determined by measuring serum fT4 and TSH levels at regular intervals (once a week). Based on our routine protocol, all patients admitted to the NICU were diagnosed and treated according to this guideline[10-12,21]. The patients who were followed by two Neonatologist (DY, CT) were included in this study. Data collection was performed by two Neonatologist (UC, AUT).

Blood samples obtained from venous blood on postnatal 5th day were centrifuged (at 4 degrees room temperature, 3000 rpm for 10 minutes) and serum samples were obtained. fT4 and TSH levels were measured from serum samples by electrochemiluminescence immunoassay method (Roche e60 analyzer, Roche diagnostic GmbH, Mannheim, Germany). All patients were divided into two groups as SGA and non-SGA. Demographic, clinical, fT4 and TSH levels were compared between SGA and non-SGA groups.

Statistical analysis

Statistical analyzes of the data were performed with the SPSS 18 (Statistical Package for Social Sciences) (version 18, SPSS Inc., St. Louis, MO, USA) package program. The conformity of the data to the normal distribution was evaluated with the Kolmogorov-Smirnov test. The t test was applied for continuous variables. Pearson χ 2 test was used for the analysis of nominal variables. Results were expressed as mean ± standard deviation or median (minimum-maximum). The results obtained from the categorical variables were expressed as frequency and percentage. P value <0.05 was interpreted as statistically significant. The power calculation was performed according to the data from a previous study[2]. A total sample size of 112 (56 patients for the SGA group, 56 patients for the AGA group) was calculated as sufficient to detect a power of 80% and a significance level of 5%.

RESULTS

During the study period, 1034 newborn infants were admitted to the NICU. 591 infants with >30 weeks of gestation and 13 newborns with congenital anomalies were excluded from the study. According to the study criteria, a total of 430 premature infants born at ≤30 weeks were included in this study. The mean GW of the patients was 28.3±1.1 weeks and BW was 1060±158 g. A total of 72 preterm newborns were recorded as SGA and 358 preterm newborns were allocated as non-SGA. The frequency of SGA was 16.7% (72/430). There was no significant difference between the groups in terms of maternal age, maternal thyroid disease, antenatal steroid administration, GW, modes of delivery, gender, and Apgar scores at 1st and 5th minute (p>0.05). BW in the SGA group (730±134 g) was significantly lower than the BW in the non-SGA group (1122±183 g) (p<0.05) (Table 1).

Table 1. Relationship between demographic characteristics and small for gestational age

Variables	SGA, n=72	Non-SGA, n= 358	P values
fT4, ng/dl [a]	1.04±0.30	1.24±0.33	0.029*
TSH, uIU/L [a]	9.91±5.6	6.60±5.2	0.012*
CH, [b]	2 (2.7)	12 (3.3)	0.461
ENS [b]	3 (4.1)	12 (3.3)	0.958
LNS [b]	14 (19.4)	71 (19.8)	0.189
RDS, [b]	45 (62.5)	210 (68.6)	0.546
IVH (evre ≥3), [b]	9 (12.5)	33 (9.2)	0.099
PDA, [b]	27 (37.5)	123 (34.3)	0.611
ROP, [b]	8 (11.1)	22 (6.1)	0.061
BPD, [b]	55 (13.8)	55 (15.3)	0.539
NEC, (evre≥2), [b]	4 (5.5)	9 (2.5)	0.064
NICU stay (days), [a]	57.9±42.2	53.6±29.9	0.299
Mortality, [b]	26 (36.1)	49 (13.6)	<0.001*

[a] mean ± standard deviation, [b] n (%), [c] median (minimum-maximum),
SGA: small for gestational age. * P <0.05 was considered statistically significant

There was no statistically significant difference between the groups in terms of ENS, LNS, RDS, IVH, PDA, ROP, BPD, NEC, and length of hospital stay (p>0.05). The mortality rate in the SGA group (36.1%) was significantly higher than the non- SGA group (13.6%) (p<0.001). The results were similar in terms of the frequency of CH in both groups (p>0.05). Serum fT4 level was significantly lower in the SGA group (1.04±0.30 ng/dL) compared to the non-SGA group (1.24±0.33 ng/dL) (p=0.029). The serum TSH level was higher in the SGA group (9.91 ± 5.6 uIU/L) than in the non-SGA group (6.6 ± 5.2 uIU/L) (p=0.012) (Table 2).

Table 2. Relationship of clinical outcome and laboratory characteristics with small for gestational age

Variables	SGA, n=72	Non-SGA , n= 358	P values
Maternal age (years), [a]	30.3±6.7	29.7±6.3	0.586
Maternal thyroid disease , [b]	1 (1.4)	9 (2.5)	0.162
Antenatal steroid, [b]	42 (58.3)	237 (66.2)	0.554
Gestational age (weeks), [a]	28.4±0.9	28.3±1.2	0.088
Birth weight (g), [a]	730±134	1122±183	<0.001*
Cesarean delivery, [b]	61 (84.7)	293 (81.8)	0.110
Apgar score, 1. min., [c]	5 (1-7)	6 (1-8)	0.071
Apgar score, 5. min., [c]	8 (4-9)	8 (3-10)	0.224
Male gender, [b]	38 (52.7)	200 (55.8)	0.213

[a] mean ± standard deviation, [b] n (%); * P <0.05 was considered statistically significant
BPD: bronchopulmonary dysplasia, CH: congenital hypothyroidism, ENS: early neonatal sepsis, GNS: late neonatal sepsis, IVH: intraventricular hemorrhage, LNS: late neonatal sepsis, NEC: necrotizing enterocolitis, PDA: patent ductus arteriosus, RDS: respiratory distress syndrome, ROP: retinopathy of prematurity, SGA: small for gestational age, fT4: free thyroxine, TSH: thyroid stimulating hormone, NICU: neonatal intensive care unit

DISCUSSION

Normal levels of thyroid hormones are important for both intrauterine and postnatal normal development. In our study, the frequency of CH was investigated in premature babies with a gestational age of ≤30 weeks. The frequency of CH was similar between preterm infants with and without SGA. However, infants with SGA had lower fT4 levels and higher TSH levels than infants without SGA. Additionally, mortality was found to be higher in infants with SGA. Results were similar between the groups in terms of demographic and clinical outcomes, except birth weight.

Preterm infants have higher mortality than term infants. However, mortality in premature infants with

SGA increases even more, as in our results[2]. There are different results regarding the effect of being premature and SGA on morbidity due to prematurity. In our results, premature babies with SGA were not found to be at risk in terms of morbidity compared to babies without SGA. There are similar or different results to our findings in the literature. We speculate that the variations might arise due to difference in number of patients, BW and GW of patients[2,21,22].

Thyroid dysfunction may cause adverse clinical outcomes in the childhood age group and may be associated with other endocrine problems[24,25]. Immature hypothalamo-pituitary-thyroid axis and thyroid dysfunction are frequently encountered in newborn babies and especially in premature babies (11). Although the relationship between CH and its morbidities in premature babies has been evaluated, the effect of CH on morbidity is still unknown[6-10]. It is known that newborn babies with SGA are at risk for endocrine problems in their advanced ages[26]. Although the effect of thyroid hormones on growth is well known, the number of studies on thyroid hormone and hypothyroidism, especially in infants with intrauterine growth restriction such as SGA, is limited[2,5,23,26]. In our country, there is no study evaluating the thyroid functions of premature babies with SGA. In this sense, our study is the first study conducted in our country.

The primary result of our study was that infants with and without SGA had a similar risk for CH. However, a higher serum TSH level and a significantly lower fT4 level were found in babies with SGA compared to babies without SGA. Similar to our results, Franco et al. found higher TSH concentrations and lower fT4 concentrations in SGA infants compared ton on-SGA[26]. It was thought that the reason for these results in premature infants with SGA was due to TSH elevation associated with transient hypothyroxinemia (27,28). In infants with SGA, control thyroid function tests mostly reach normal values after thyroid function tests performed on the 5th day. The frequency of CH was found to be similar in infants with and without SGA, as controlled thyroid functions were mostly measured as normal. Thus, this condition in babies with SGA is defined as transient hyperthyrotropinemia[23]. It has been reported that transient hyperthyrotropinemia is more common in babies born before 30 weeks of gestation, in addition to babies with SGA, compared to term babies (28). In our results, the frequency of CH was found to be similar in both groups, which supported the presence of transient hyperthyrotropinemia in our patients.

In previous studies, the cause of high TSH and low fT4 levels in babies with SGA compared to babies without SGA was attributed to fetal hypoxemia, impaired fetal nutrition and abnormal thyroid function associated with SGA[2,5,29]. It is presumed that malnutrition may lead to hypothyroxinemia as a result of affecting thyroid hormone synthesis by decreasing the availability of phenylalanine and tyrosine[2,12]. In addition, hypothyroxinemia is probably temporary in infants with SGA, and it is thought that thyroid function improves with the improvement of postnatal nutrition[2]. It was found that TSH concentrations were significantly higher in older ages in children born with SGA, TSH levels were close to the upper limit of the normal range in 20% of children with SGA, but there was no difference in fT4 levels[30,31]. Although childhood thyroid hormone values could not be evaluated in our results, it would be concluded that TSH elevation may play a similar role at different stages of the developmental process[5].

Since thyroid hormones are associated with important physiological functions, the etiology and effect of higher TSH levels in SGA infants on growth should be investigated. Immaturity of the hypothalamo-pituitary-thyroid axis may be associated with many factors such as intrauterine stress, less efficient thermogenic response, or non-thyroid diseases. It can be quite difficult to distinguish this disorder between SGA and non-SGA infants[5].

In a previous study, it has been reported that infants with high TSH levels had lower verbal IQ scores and worse neurological outcomes in childhood[32,33]. However, the clinical significance of neonatal TSH elevation is still debated. Considering the possible cognitive risks in infancy and childhood, preterm infants with SGA who have elevated TSH should be followed closely[2,5]. Additionally, premature infants with SGA may be at risk of being mistakenly diagnosed and treated with CH due to transient hyperthyrotropinemia. Attending clinicians should be careful in terms of transient hyperthyrotropinemia (high TSH) in premature infants with SGA. Therefore, our results suggested that premature infants with SGA were prone to transient thyroid dysfunction and should be followed closely. Furthermore, neonatal screening tests based solely on measuring TSH levels cannot diagnose transient hypothyroidism. Therefore, it is recommended to

measure both fT4 and TSH in screening tests, especially in premature babies with SGA[5].

Our study had some limitations as it was retrospective and conducted in a single-center. Our case number was relatively small compared to large-scale studies. Therfore, further studies with more number of cases were required to confirm our findings. Our results may not be generalizable to other populations as we had only one center data. Moreover, factors such as the clinical status of the patients that could affect the thyroid functions, the drugs received for the newborns, the drugs administered to the mothers, and the thyroid antibody values could not be evaluated. Finally, the data of the follow-up results of thyroid function tests during the hospitalization of the patients could not be examined.

In conclusion, premature newborns with SGA may have a transient TSH elevation and fT4 decrease compared to non-SGA babies. These temporary thyroid function test results do not pose a risk in terms of the frequency of CH in SGA infants. Periodic thyroid function test follow-up, endocrinological evaluation and neurological development should be closely followed in premature babies with SGA who have these features.

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