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Non-Thyroidal Illness Syndrome in Neonatal Intensive Care Units

Yenidoğan Yoğun Bakım Ünitesinde Tiroid Dışı Hastalık Sendromu

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ABSTRACT

Objective: This study aims to establish the incidence of non-thyroidal illness syndrome (NTIS) in newborns and investigate its potential impact on neonatal outcomes. Additionally, by identifying the risk factors associated with the development of NTIS, this study aims to deepen the understanding of the condition.

Materials and Methods: A total of 337 patients in the neonatal intensive care unit were studied retrospectively. Data on demographic and clinical characteristics, including gestational age, birth weight, head circumference, height, Apgar score, SNAPPE score, presence of congenital anomalies, mode of delivery, respiratory support, and duration of hospitalization, were collected. All patients underwent measurement of TSH and free T4 levels.

Results: The study found that 4.5% of patients were diagnosed with NTIS. Patients with NTIS had higher rates of preterm delivery. NTIS patients exhibited lower gestational age, birth weight, head circumference, height, and Apgar scores than non-NTIS patients. NTIS patients had significantly more extended hospital stays, but no differences in mechanical ventilation duration or SNAPPE scores were obtained.

Conclusions: This study indicates that thyroid dysfunction can occur in critically ill newborns, highlighting the necessity of evaluating thyroid function in this demographic.

Keywords: Euthyroid sick syndrome, neonatal intensive care unit, non-thyroidal illness syndrome, thyroid function tests, thyroid screening

ÖZ

Amaç: Bu çalışmanın amacı yenidoğanlarda tiroid dışı hastalık sendromunun (TDHS) yaygınlığını belirlemek ve yenidoğan sonuçları üzerindeki potansiyel etkilerini araştırmaktır. Ayrıca, TDHS gelişimi ile ilişkili risk faktörlerini belirleyerek, sendromun daha iyi anlaşılmasına katkıda bulunmak amaçlanmaktadır.

Materyal ve Metot: Yenidoğan yoğun bakım ünitesinde yatan 337 hastanın verileri retrospektif olarak toplandı. Gebelik yaşı, doğum ağırlığı, Apgar skoru, SNAPPE skoru, doğum şekli, konjenital anomaliler, solunum desteği ve hastanede yatış süresi gibi demografik ve klinik veriler toplanmıştır. Tüm hastalarda tiroid uyarıcı hormon (TSH) ve serbest tiroksin (sT4) düzeyleri ölçülmüştür.

Bulgular: Çalışmaya alınan hastaların %4,5'inde TDHS saptanmıştır. TDHS tanısı alan hastalar, daha düşük gebelik haftası, doğum ağırlığı, baş çevresi, boy, ve Apgar skorlarına sahipti. TDHS hastalarının hastane yatış süreleri anlamlı şekilde daha uzun bulunmuş, ancak mekanik ventilasyon süresi ve SNAPPE skorlarında fark gözlenmemiştir.

Sonuç: Bu çalışma, kritik hastalık geçiren yenidoğanlarda tiroid fonksiyon bozukluklarının görülebileceğini ve bu grubun tiroid fonksiyonlarının değerlendirilmesinin önemli olduğunu göstermektedir.

Anahtar Kelimeler: Tiroid dışı hastalık sendromu, tiroid fonksiyon testleri, tiroid taraması, ötiroid hasta sendromu, yenidoğan yoğun bakım ünitesi

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INTRODUCTION

Thyroid hormones play a vital role in brain development throughout the postpartum period. After birth, serum levels of thyroxine (T4) and triiodothyronine (T3) rise significantly, supporting the somatic growth and maturation of the newborn. Low thyroid hormone levels during early life can negatively affect growth and development, potentially resulting in irreversible cognitive impairment due to brain injury.[1,2]

Endocrine disorders caused by underlying diseases, stress, or medications are frequently observed in critically ill patients.[3] Particularly in premature infants, the immaturity of the thyroid axis, maternal and fetal medications, and prematurity-related morbidities all increase the likelihood of abnormalities in thyroid function tests (TFT).[4]

Altered thyroid hormone phenomenon, known as non-thyroidal illness syndrome (NTIS), refers to a distinct pattern of hormonal changes in the pituitary –thyroid axis in patients without primary thyroid disease.[5,6] There is ongoing debate about whether this hormonal alteration represents an adaptive protective response or a maladaptive process that may warrant therapeutic intervention.[7,8]

Several studies have reported associations between TFT abnormalities and the development of severe illness and poor clinical outcomes.[9] Therefore, early screening for thyroid dysfunction and appropriate clinical evaluation are essential in neonates admitted to neonatal intensive care units (NICU).

The goal of this study is to establish the prevalence of NTIS in newborns and to investigate its potential impact on neonatal outcomes. In addition, by identifying risk factors that are linked to the onset of NTIS, this study seeks to improve the understanding of the disorder.

MATERIALS AND METHODS

Ethics Committee Approval: The study was performed in compliance with the Declaration of Helsinki. The study methodology was approved by the Ethics Committee of Bakirkoy Sadi Konuk Training and Research Hospital (Date: 29.05.2017, decision no: 2017-04-22), and all anonymized data linked to the study are accessible upon reasonable request.

The study enrolled 337 patients aged 0 to 1 month at Bakirkoy Sadi Konuk Training and Research Hospital NICU. Clinical and demographic data were retrospectively acquired from the hospital's computerized information management system and patient records. Gestational weeks, birth weights, diagnoses, Apgar score[10], Score for Neonatal Acute Physiology with Perinatal Extension (SNAPPE),[11] genders, mode of delivery, presence of congenital anomalies, the requirement of respiratory support, inotropic agents or phototherapy, duration of hospitalization, the requirement for inotropes or transfusions prior to evaluation and outcomes was recorded. The SNAPPE score is a scale calculated within the first 24 hours using physiological and perinatal data to predict the risk of mortality in neonates.[11] The incidence of postpartum surgical procedures and the mother's chronic illness were also noted. Thyroid-stimulating hormone (TSH) and free thyroxine (fT4) values were obtained for all hospitalized patients. Patients were classified into three groups according to the timing of thyroid function tests: 0-7 days, 8-15 days, and 16-30 days. The diagnosis of NTIS was made when patients with abnormal thyroid function test values showed improvement in control values. Control values were obtained after 15 days for all patients. The control TFT values for 21 deceased patients could not be collected due to their poor clinical status, resulting in their exclusion from the research.

The last menstrual period (LMP) reported by the mother or the modified Ballard score was used to ascertain the gestational age of all preterm neonates.[12] Infants below 37 weeks of gestation were classified as premature, while those at 42 weeks or above were considered post-term. The evaluation of growth was conducted by employing Lubchenko's growth curves, and infants with height, weight, and head circumference values below the 10th percentile for their respective gestational ages were categorized as small for gestational age (SGA). In contrast, newborns with measurements exceeding the 90th percentile were categorized as large for gestational age (LGA) relative to their gestational age.

The analysis of hormone levels for free triiodothyronine (fT3), fT4, and TSH was conducted using the electrochemiluminescence immunoassay (ECLIA) method from patient serum, with a Roche Elecsys E170 device employed for this purpose. The reference range of thyroid tests was 0.43-16.1 mIU/L and 0.83-3.09 ng/dL for TSH and fT4, respectively.

Statistical Analysis: The data collected in this research were analyzed utilizing the SPSS 20.0 software program for Windows. Continuous variables adhering to a normal distribution were represented as mean±standard deviation, whilst non-normally distributed data were conveyed as median (minimum -maximum) values. The distribution's normality was assessed by using histograms and the Kolmogorov-Smirnov test. Categorical variables were represented as counts (percentages). The importance of the disparities between the two group means in independent samples was evaluated utilizing the Mann-Whitney U test for non-normally distributed data and the Student's t-test for regularly distributed data. In instances of repeated measurements, the Wilcox-

on test was utilized for non-normally distributed data in pair-wise group comparisons, and the Friedman test was utilized for multiple groups exceeding two. Results were deemed statistically significant if their p-values were below 0.05.

RESULTS

The study recruited a total of 337 patients. Of these, 60.2% (n=203) were male. Cesarean section was conducted in 59.3% (n=200) of these cases. Among the patients, 86.3% were classified as appropriate for gestational age (AGA), 6,2% as SGA, and 7,7% as LGA. Furthermore, 43% (n=145) of the patients were preterm, while 56.9 % (n=192) were term infants. The median birth weight was 2880 grams (690 -4670 g), and the median length of hospitalization was 9 days (1-273). The average SNAPPE score was found to be 15 (1-59), and the median length of mechanical ventilation was determined to be 5 (1-76) days (Table 1).

Out of the fifteen patients (4.5%) diagnosed with NTIS, all of them were AGA. When the relationship between NTIS and prematurity was examined, the prevalence of NTIS was found to be 1.6% in term infants and 8.3% in preterm infants. NTIS was significantly more common in preterm infants compared to term infants (p = 0.007). This finding suggests that prematurity may be associated with an increased risk of developing NTIS (Table 2).

The study's findings indicated that patients diagnosed with NTIS exhibited lower gestational week, head circumference, birth weight, and height ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$ consecutively). In NTIS patients, A lower Apgar score was observed at 1 and 5 minutes ($p=0.005$, $p=0.007$). Furthermore, patients with NTIS had considerably longer hospital stays and needed oxygen support, as demonstrated in Table 2 ($p=0.001$, $p=0.001$). The two groups did not demonstrate any substantial disparities in terms of lactate levels, SNAPPE scores, or the duration of mechanical ventilation. NTIS was more prevalent in patients diagnosed with sepsis (p = 0.033). Gender, mode of delivery, presence of chronic maternal disease, and frequency of postpartum surgical procedures were similar between groups. Patients with and without NTIS exhibited similar features regarding the presence of congenital anomalies, transfusion prior to the evaluation, use of inotropic agents, and requirement of phototherapy (Table 3).

Table 1. Clinical features of patients.

Gender, male, n (%)		203 (60.2)
Birth weight (gr), median (min-max)		2880 (690-4670)
Birth height (cm), median (min-max)		48 (26-56)
Birth head circumference (cm), median (min-max)		34 (20-39)
Gestation Week, median (min-max)		37 (21-42)
Cesarean section n, (%)		200 (59.3)
Prematurity (≤36 gestational week), n (%)		145 (43.0)
Birth weight for gestational age, n (%)	AGA	290 (86.0)
	SGA	26 (7.71)
	LGA	21 (6.23)
Apgar at 1 minute, median (min-max)		8 (0-9)
Apgar at 5 minutes, median (min-max)		9 (1-10)
SNAPPE score, median (min-max)		15 (1-59)
Duration of mechanical ventilation (day), median (min-max)		5 (1-76)
Length of hospitalization at NICU (day), median (min-max)		9 (1-273)

AGA: Appropriate for gestational age; SGA: Small for Gestational Age; LGA: Large for Gestational Age; SNAPPE score: Score for neonatal acute physiology with perinatal extension; NICU: Neonatal intensive care unit

Table 2. Association between gestational age and the presence of non-thyroidal illness syndrome.

		No NTIS	NTIS	p
Gestational week, n (%)	**≤36**	133 (91.7)	12 (8.3)	**0.007**
	>36	189 (98.4)	3 (1.6)	

NTIS: Non-thyroidal illness syndrome.

Table 3. Clinical features of patients with and without non-thyroidal illness syndrome.

Clinical features		No NTIS	NTIS	p
Gestation week, median (min-max)		37 (23-42)	28 (25-38)	**0.001**
Birth weight (gr), median (min-max)		2900 (690-4670)	1080 (750-3520)	**0.001**
Birth height (cm), median (min-max)		48 (25-56)	36 (32.5-50)	**0.001**
Birth head circumference (cm), median (min-max)		34 (20-39)	27 (24-35)	**0.001**
Gender, n (%)	**Female**	131 (%97.8)	3 (%2.2)	0.110
	Male	191 (%94.1)	12 (%5.9)	
Mode of delivery, n (%)	**NVD**	132 (%96.4)	5 (%3.6)	0.555
	C/S	190 (%95.0)	10 (%5.0)	
Apgar at 1 minute, median (min-max)		8 (0-9)	5 (1-9)	**0.005**
Apgar at 5 minute, median (min-max)		9 (3-10)	8 (2-10)	**0.007**
SNAPPE score, median (min-max)		14.5 (1-59)	18 (12-32)	0.561
Duration of mechanical ventilation (day), median (min-max)		5 (1-76)	11 (1-48)	0.235
Requirement of supplemental oxygen (L/Min), median (min-max)		3 (1-19)	16 (2-24)	**0.001**
Length of hospitalization at NICU (day), median (min-max)		10 (2-273)	62 (2-136)	**0.001**
Lactic acid on admission (mmol/L), median (min-max)		1 (0.9-6.1)	1 (0.9-1.7)	0.255
Requirement of inotropic agents, n (%)		16 (88.9)	2 (11.1)	0.123
Presence of congenital anomaly, n (%)		19 (100)	0	0.411
Requirement of transfusion prior to evaluation, n (%)		16 (88.9)	2 (11.1)	0.188
Requirement of phototherapy, n (%)		77 (92.8)	6 (7.2)	0.167
Requirement of postpartum surgical procedure, n (%)		13 (86.7)	2 (13.3)	0.139
Presence of sepsis		14 (82.4)	3 (17.6)	**0.033**

NTIS: Non-thyroidal illness syndrome; NVD: Normal vaginal delivery; C/S: Cesarean section; SNAPPE score: Score for neonatal acute physiology with perinatal extension; NICU: Neonatal intensive care unit

During the first week of life, both fT4 and TSH levels were significantly lower in preterm infants compared to term infants (p = 0.024 and p = 0.016, respectively). This suggests that thyroid hormone suppression is more prominent in preterm neonates during the early neonatal period. However, no statistically significant differences were observed between the two groups in fT4 and TSH levels during the 8–15 and 16–30 day intervals (p >0.05 for all comparisons), indicating that the divergence in thyroid function is most marked during the first week after birth (Table 4).

Table 4. Comparison of thyroid function test values between preterm and term infants by sampling day.

Parameters		Prematurity (≤36 gestational weeks	Term (>36gestational weeks)	p
0-7 days, median (min-max)	fT4 (ng/dL)	1.295 (0.64-2.08)	1.38 (0.46-2.74)	**0.024**
	TSH (µIU/mL)	3.425 (0.65-45.28)	4.545 (0.22-38.34)	**0.016**
8-15 days, median (min-max)	fT4 (ng/dL)	1.295 (0.3-2.07)	1.37 (0.77-9.0)	0.071
	TSH (µIU/mL)	3.190 (0.64-19.69)	3.35 (0.55-68.11)	0.954
16-30 days, median (min-max)	fT4 (ng/dL)	1.154 (0.62-2.07)	1.19 (0.77-1.66)	0.768
	TSH (µIU/mL)	3.46 (0.91-22.97)	3.51 (0.73-22.5)	0.948

fT4: free thyroxine; TSH: Thyroid-stimulating hormone.

Thyroid function test results of all patients included in the study are presented in Table 5 according to the timing of sample collection (days 0–7, 8–15, and 16 –30). For each time interval, median values and corresponding minimum–maximum ranges of fT4 and TSH levels are reported (Table 5).

Table 5. Thyroid function test values by sampling time in all patients.

Parameters		Median (min-max)
0-7 days, median (min-max)	fT4 (ng/dL)	1.34 (0.46-2.74)
	TSH (μIU/mL)	3.87 (0.22-45.28)
8-15 days, median (min-max)	fT4 (ng/dL)	1.33 (0.3-9)
	TSH (μIU/mL)	3.32 (0.55-68.11)
16-30 days, median (min-max)	fT4 (ng/dL)	1.19 (0.62-2.07)
	TSH (μIU/mL)	3.46 (0.73-22.97)

fT4: free thyroxine; TSH: Thyroid-stimulating hormon

DISCUSSION AND CONCLUSION

TFTs are significant biomarkers linked to disease severity and therapy efficacy in both adult and pediatric populations. Studies indicate that thyroid hormone levels serve as a predictive marker for certain serious disorders. Specifically, alterations in TSH, fT4, and fT3 concentrations may be important for forecasting disease advancement and therapeutic response.[13,14]A study by Goldsmith et al. found that lower T3 and T4 levels in sick term newborns were linked to prolonged mechanical ventilation, elevated lactate levels, and higher SNAPPE scores. The study also demonstrated that the group with combined low T3, T4, and TSH levels had the highest fatality rate, highlighting that impaired thyroid function may significantly influence prognosis and outcomes in sick neonates.[9] Hammati et al.'s study revealed a significant decrease in fT3 levels during critical illness, although no notable changes were observed in fT4 and TSH levels. This study found no significant link among the length of mechanical ventilation, the existence of congenital heart disease (CHD), and the levels of fT3 and fT4.[15] Another study found that fT4 levels were not associated with mortality but were correlated with a prolonged hospital stay. Additionally, male gender, vaginal delivery, hypoxic-ischemic encephalopathy, and the need for mechanical ventilation exceeding 24 hours were recognized as risk factors.[16] Collectively, these studies underscore the importance of evaluating thyroid function in sick-term newborns, as abnormalities in thyroid hormone levels correlate with negative clinical outcomes, prolonged hospital stays, increased need for interventions, and elevated mortality rates. The present study reinforces these observations by showing that NTIS was associated with significantly lower Apgar scores, birth weight, and gestational age, along with increased oxygen demand and longer hospitalization.

Hypothyroxinemia is prevalent among preterm newborns.[17,18] The significance of thyroid hormones in brain development is well-documented. Nonetheless, the consequences of hypothyroxinemia in preterm infants are not fully understood. There is ongoing discourse surrounding the necessity of levothyroxine treatment for premature infants with hypothyroxinemia.[19,20] A study specifically investigating hypothyroxinemia in premature infants concluded that 14.5% of preterm births exhibited hypothyroxinemia. Additionally, 92% of these cases were observed in preterm infants born prior to 32 weeks of gestation and weighing under 1500 grams. Consequently, the recommendation was made for the implementation of early screening for hypothyroxinemia in this specific group of preterm infants.[21] According to the Yoon et al. study, transient hypothyroxinemia in newborns with extremely low birth weight is linked to higher composite morbidities and mortality. Furthermore, the initially measured T4 level was identified as a more effective predictor of outcomes in these patients.[22] In accordance with extant literature, the present study disclosed that 80% of patients with the condition were preterm infants. Furthermore, patients diagnosed with NTIS exhibited a lower gestational age and reduced birth weight, which were statistically significant.

Perinatal asphyxia has been shown to impair cellular function across multiple organs, leading to reduced oxidative phosphorylation and ATP production. Hence, it is essential to acknowledge the critical influence of prenatal hypoxia on thyroid function.[23] Thyroid dysfunction has been observed in asphyxic neonates in previous studies. A study investigating the effects of birth asphyxia on thyroid hormones demonstrated a notable decline in TSH levels post-asphyxia, with the magnitude of the reduction corresponding with the severity of asphyxia.[24] A separate investigation revealed a decline in TFT levels in asphyxiated newborns at 18 and 24 hours after birth.[25] Our investigation revealed that the Apgar score of NTIS patients was significantly lower compared to those without NTIS. In our opinion, thyroid

hormone levels should be closely monitored in asphyxia patients.

The incidence of NTIS is increased in sepsis. The study by El-Nawawy et al. underscores the high prevalence of NTIS among pediatric patients with shock and illustrates the relationship between thyroid hormone dysfunction and disease severity.[26] Likewise, research conducted by Xu et al. indicates a significant frequency of NTIS in pediatric patients with sepsis. This study observed a negative correlation between interleukin-6 (IL-6) levels and T3 and T4 levels, highlighting the impact of inflammatory cytokines on thyroid hormone regulation.[27] Consistent with the previous literature, our investigation also identified a greater prevalence of sepsis in patients with NTIS. Taken together, these findings suggest that NTIS is not only a biochemical phenomenon but also a potential indicator of systemic disease severity in neonates. This reinforces the need to assess thyroid function not solely as routine screening, but as an integrated part of neonatal critical care evaluation.

The study's limitations can be attributed to two factors: firstly, the small number of patients included, and secondly, the retrospective natures of the research design. The inability to assess fT3 levels in certain NTIS patients, along with the exclusion of those who died before a thyroid evaluation could be performed, represents additional limitations of the study. These variables may have led to the underrepresentation of NTIS cases and limited the examination of the correlation between NTIS and mortality.

In conclusion, our study highlights the importance of timely and comprehensive thyroid function evaluation in neonates, particularly those who are preterm or critically ill. Identifying and understanding the early hormonal patterns associated with NTIS may contribute to improved risk stratification and clinical outcomes. Further prospective studies are warranted to clarify whether thyroid hormone abnormalities in this population are simply markers of illness severity or modifiable therapeutic targets.

Ethics Committee Approval: The study was approved by the Ethics Committee. (Date: 29.05.2017, decision no: 2017-04-22).

Conflict of Interest: No conflict of interest was declared by the authors.

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