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Thyroid Hormones as Potential Prognostic Markers for Neonates with Hypoxic İschemic Encephalopathy

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ABSTRACT:
Purpose: Hypoxic ischemic encephalopathy (HIE) is one of the most important causes of mortality and morbidity in newborns. Few studies with conflicting results have been conducted on the effect of perinatal asphyxia and thyroid hormones.
Material and methods: A total of 96 newborns (46 patients with HIE and 50 controls) were included in the study. Electroencephalography (EEG) results, cranial magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), Sarnat Stages, and the presence of seizures of the HIE group were recorded. Thyroid stimulating hormone (TSH) and free thyroxine (fT4) levels of all cases were also measured between 5-10 days. Patients with HIE were separated into 3 groups according to the fT4 (≤1.52 ng / dL, 1.52-1.84 ng / dL, and ≥1.84 ng / dL), and TSH (≤2.56 IU / mL. 2.56-5.3 1IU / Ml, and ≥5.31 IU / mL) levels.
Results: All the newborns with seizures were in the 1st or 2nd tertiles of fT4, none of those with high fT4 (>1.84 ng/dL), and the difference was statistically significant (x^2=6.61; p=0.036). A negative correlation was determined between fT4 level and duration of hospitalization (=-0.43; p=0.03), duration of respiratory support (r=-0.32; p=0.029), duration of intubation (r=-0.40; p=0.006), and time to full oral feeding (r=-0.40; p=0.006). The TSH level was only correlated with the duration of hospitalization (r=-0.34, p=0.02).
Conclusion: Free T4 level may be used as a prognostic marker in newborns with HIE. Further multicenter, larger, and prospective studies are needed to support and confirm these findings.
Keywords: *Newborn, Hypoxic ischemic encephalopathy, Hypothermia, Thyroid hormones*

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INTRODUCTION

Hypoxic Ischemic Encephalopathy (HIE) is a heterogeneous syndrome, which manifests with difficulty starting and generally maintaining respiration in an infant together with cognitive disorder, tonus, and reflex loss or seizures (Burn et al., 2014; Martinello et al., 2017). The frequency of neonatal encephalopathy associated with perinatal asphyxia is approximately 1-8/1000 live births (Kurinczuk et al., 2010).

The basic mechanisms leading to neuronal death after hypoxia-ischaemic reperfusion are initiated with energy depletion and activation of glutamate receptors, subsequently increased cytosolic calcium levels cause cellular damage (Volpe, 2001). The primary event in the pathophysiology of perinatal asphyxia is impaired ventilation at pulmonary level because of insufficient gas exchange or prenatal events in the placenta. Consequently, oxygen and carbon dioxide exchange are impaired, so arterial hypoxemia, hypercarbia, and acidosis develop. Changes in cerebral blood flow associated with

asphyxia, and cellular and metabolic changes in the central nervous system are important in the prognosis of the patients (Perlman, 2006; Tan, 2021). Therapeutic hypothermia is the only proven method in the treatment of perinatal asphyxia. Every decrease of 1°C in body temperature causes a reduction of 6-10% in brain metabolism. Thus it is possible to prevent or reduce cellular and metabolic changes which can damage the brain (lang et al., 2007).

Thyroid hormones have a critical role in basal metabolic rate. Adenosine triphosphate (ATP) formation increases with the effect of thyroid hormones, so an increase is observed in oxygen and energy consumption. In the absence of thyroid hormones, the basal metabolic rate falls (Yalçın and Besler, 2016). In other words, thyroid hormones are responsible for preserving the energy homeostasis of the body. On the other hand, the main goal in the treatment of hypothermia is to maintain this homeostasis by reducing the basal metabolic rate. Thyroid functions have been reported to be lower after the birth of HIE patients, especially in those with moderate or severe HIE (Kobayashi et al., 2018; Pereira et al., 2003).

The relationship between thyroid function and neurological outcomes in HIE patients is not well known (Kobayashi et al., 2018). Kobayashi et al. suggested that brain damage in asphytic neonates could be predicted with serum fT3 and FT4 levels after the third postnatal day (Kobasyashi et al., 2018). Few studies have been conducted on the effect of perinatal asphyxia on thyroid hormones, and the studies in the literature have presented with conflicting results, most likely because of differences in the methodological design (Borges et al., 1985; Franklin et al., 1985; Pereira et al., 2003). The aim of this study was to investigate thyroid functions as a prognostic factor in the evaluation of newborns exposed to asphyxia.

MATERIAL and METHODS

This study included 46 cases applied with total body cooling for the treatment of HIE, and TSH and fT4 levels measured at 5-10 days in the Neonatal Intensive Care Unit of the tertiary level Research and Applications Hospital of Sivas Cumhuriyet University between January 2018 and January 2021. A control group of 50 cases was selected from those with similar gestational age and birth weight who brought at the Neonatal outpatient clinic for routine check-up.

Diagnostic Criteria in Hypoxic-İschemic Encephalopathy (Akisu et al., 2018)

10th minute Apgar score <5 or need for ongoing resuscitation,

Fetal umbilical blood gas pH <7.00 or BE<-12 mmol/L,

Visualization of brain damage compatible with HIE on brain MRI or MRS,

Multiple organ failure or effects on organs.

Inclusion Criteria and Exclusion Criteria

Inclusion Criteria:

Gestational age ≥36 weeks and ≤6 hours postnatal,

pH≤7.00 or BE ≤-16 mmol/L in the first hour or in the cord blood gas,

10th APGAR score <5 with the continuing need for resuscitation,

Findings of moderate or severe encephalopathy in clinical evaluation.

Exclusion Criteria:

Infants with maternal chorioamnionitis,

Infants older than 6 hours postnatal,

Infants born before <36 weeks and birthweight <2000 g,

Infants with congenital metabolic disease,

Infants with very severe or widespread cranial parenchymal bleeding,

Infants with very sever e life-threatening coagulopathy,

Infants with trisomy 13, trisomy 18, or multiple organ anomalies.

For the grading of HIE, the Sarnat and Sarnat evaluation was applied (Sarnat and Sarnat, 1977). Patients with grade 2 and grade 3 HIE were applied with therapeutic hypothermia treatment for a total of 72 hours using a Tecotherm Neo ((Inspiration Healthcare, UK), (ASTEK Medikal, Turkey)) device at mean 33.5°C (33-34°C).

Patients with HIE were separated into 3 groups according to the fT4 (≤1.52 ng / dL, 1.52-1.84 ng / dL,

and ≥1.84 ng / dL), and TSH (≤2.56 IU / mL. 2.56-5.3 1IU / Ml, and ≥5.31 IU / mL) levels. The analysis of cord blood gases from the umbilical artery was measured using a blood gas analyzer (ABL 90 flex, Radiometer, Denmark). Venous blood samples were obtained from all the neonates on postnatal 5-10 days for thyroid function tests, TSH and fT4. After centrifugation at 4°C for 15 minutes at 3500 rpm, serum TSH, and fT4 levels were determined with the electrochemiluminescent immunoassay (Roche Cobas e601, Germany).

Within 1 week after the hypothermia treatment, cranial MRI and MRS examinations were made of all the patients. EEG examination was made routinely of all the patients within the first week using a 21-channel (10-20) system by Nihon Kohden (EEG 1200). The EEG characteristics (signal width, duration, and frequency content) were measured automatically using different parameters. A diagnosis of seizure was made from clinical observation and/or confirmation on EEG.

Purpose and Type of the Study

The study was a retrospective, case control design.

Sampling and Participant

This study included 46 cases applied with total body cooling for the treatment of HIE, and a control group of 50 cases selected from those with similar gestational age and birth weight who brought at the Neonatal outpatient clinic for routine check-up. All of the study groups (case and control group) were born in our hospital.

Data Collection Tools

All the patient files who was measured serum TSH and fT4 levels at 5-10 days were retrospectively evaluated. Gender, gestational age at birth, birth weight, head circumference, length, type of birth, resuscitation in the delivery room, cord blood gas values, asphyxia etiology, time of starting hypothermia, respiratory support, mechanical ventilation support, occurrence of seizure, electroencephalography (EEG) results, cranial magnetic resonance imaging (MRI), Magnetic resonance spectroscopy (MRS) results, and mortality were recorded.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS vn. 16.0 software (SPSS, Chicago, IL, USA). Conformity of the data to normal distribution was assessed with the Shapiro-Wilk test. Continuous data were stated as mean±standard deviation (SD) or median (minimum-maximum) values, and categorical data as the number (n) and percentage (%). The comparisons of qualitative data were made with the Chi-square test, and quantitative data with the Independent Samples t-test, and the Mann Whitney U-test. Correlations between quantitative data were examined with Pearson and Spearman Rank correlation analyses. A value of $p<0.05$ was accepted as statistically significant.

Ethical Approval

Approval for the study was granted by the Institutional Ethics Committee (decision no: 2020-09/07, dated: 23.09.2020). Written informed consent was obtained from all the parents before any procedure was applied.

RESULTS

Weight, length, and head circumference were similar in the study (n=46) and control (n=50) groups. Significant differences were determined between the study and control groups in respect of the percentage of cesarean section deliveries and gestational age at birth (35% vs 74%; $p<0.001$ and 39.16±1.23weeks vs 38.32±1.11 weeks; $p<0.01$, respectively). No statistically significant difference was determined between the groups in respect of TSH and fT4 levels, (5.26±4.90 IU/mL vs 5.08±4.39 IU/mL; $p>0.05$ and 1.67±0.41 vs 1.63±0.42 ng/dL; $p>0.05$). The APGAR scores of the groups were statistically significantly different as expectedly ($p<0.001$) (Table 1).

The cord blood gas, Sarnat and Sarnat classification etiology of HIE, the length of stay in Neonatal Intensive Care Unit (NICU), duration of Mechanical Ventilation (MV), duration of respiratory support, cardiopulmonary resuscitation rate, mortality rate, abnormal findings on diffusion and cranial MR, abnormal EEG findings, and seizures of the case group are shown in Table 2.

Table 1. Metabolic and anthropometric parameters of the study population.

	Hypothermia Group (N=46)	Control Group (N=50)	P
Cesarean section, n (%)	16 (35)	37 (74)	<0.001
Female, n (%)	17 (36)	23 (46)	0.24
Gestational age, week	39.16±1.23	38.32±1.11	<0.01
Maternal age, year	27,80±5,85	28,36±6,42	0.66
Weight, kg	3.24±0.53	3.18±0.47	0.60
Lenght, cm	49.42±3.2	49.26±1.87	0.75
Head circumference, cm	34.93±1.68	34.51±1.29	0.17
APGAR Score (1 min.)	3.57±2.07	7.37±0.92	<0.001
APGAR Score (5. Min.)	6.22±1.72	8.71±0.70	<0.001
TSH (IU/mL)	5.26±4.90	5.08±4.39	0.85
fT4 (ng/dL)	1.67±0.41	1,63±0.42	0.70

APGAR; Activity, Pulse, Grimace, Appearance, Respiratory. **TSH**; Thyroid-stimulating hormone. **fT4;** Free thyroxine

Table 2. Clinical characteristics of hypoxic-ischemic encephalopathy group.

	N	Mean±SD	Median (Min-Max)
Chord blood gase	46		
pH		6.93±0.10	6.95(6.68-7.15)
$PaCO_2$ (mmHg)		68.92±17.87	67.5 (40-108)
PaO_2 (mmHg)		27.74±13.39	22(15-61.9)
HCO_3 (mmol/L)		13.39±3.73	13.1(6-21.8)
Base deficit (mmol/L)		-18.04±4.37	-18(-27;-9)
Lactate(mmol/L)		10.38±3.31	10.4(1.8-16.73)
Sarnat & Sarnat Classification	46		
Moderate	38		82.6%
Severe	8		17.4%
Etiology	46		
Unknown	18		39.1%
Cord prolapsus	3		6.3%
Meconium aspiration syndrome	7		15.2%
Ablatio placenta	3		6.5%
Dystocia	15		32.6%
NICU stay, days		12.6±5.5	11.5(3-35)
Duration of respiratory support, days		4.84±4.91	4 (0-26)
MV duration, days		1.71±2.86	1(0-15)
Abnormal EEG finding	37		
Abnormal diffusion MR finding	42		12(28.6)
Abnormal cranial MR finding	42		20(%47,6)
Seizures	8		17.4%
Time of seizure, hour		45±03	18(0-120)
Hypothermia treatment start time, hours		3.13±2.15	2(1-10)
Mortality rate	2		4.3%
Cardiopulmonary resuscitation rate	17		37%
Apgar at first minute	46	3.57±2.07	4 (0-7)
Apgar at fifth minute	46	6.22±1.72	6(0-9)

EEG: Electroencephalography; MR: Magnetic resonance, **MV**: Mechanical ventilation; **NICU**: Neonatal intensive care unit; **SD**: Standart deviation.

Magnetic resonance spectroscopy and EEG findings (normal or abnormal), Sarnat Stages (2 or 3), and the presence of seizures were compared according to the 3 groups of TSH and fT4 tertiles; All the newborns with seizures were in the 1st or 2nd tertiles of fT4, none of those with high fT4 (>1.84 ng/dL), and the difference was statistically significant (x^2=6.61; p=0.036). All the other parameters according to fT4 and TSH tertiles were similar (p>0.05) (Fig. 1).

Correlations of fT4 and TSH levels with durations of hospitalization, respiratory support, and intubation, and time to full oral feeding were evaluated. A

negative correlation was determined between fT4 level and duration of hospitalization (=-0.43; p=0.03), duration of respiratory support (r=-0.32; p=0.029), duration of intubation (r=-0.40; p=0.006), and time to full oral feeding (r=-0.40; p=0.006). The TSH level was only correlated with the duration of hospitalization (r=-0.34, p=0.02). All correlations were controlled for gestational age and postnatal age at which blood was drawn (Fig. 2).

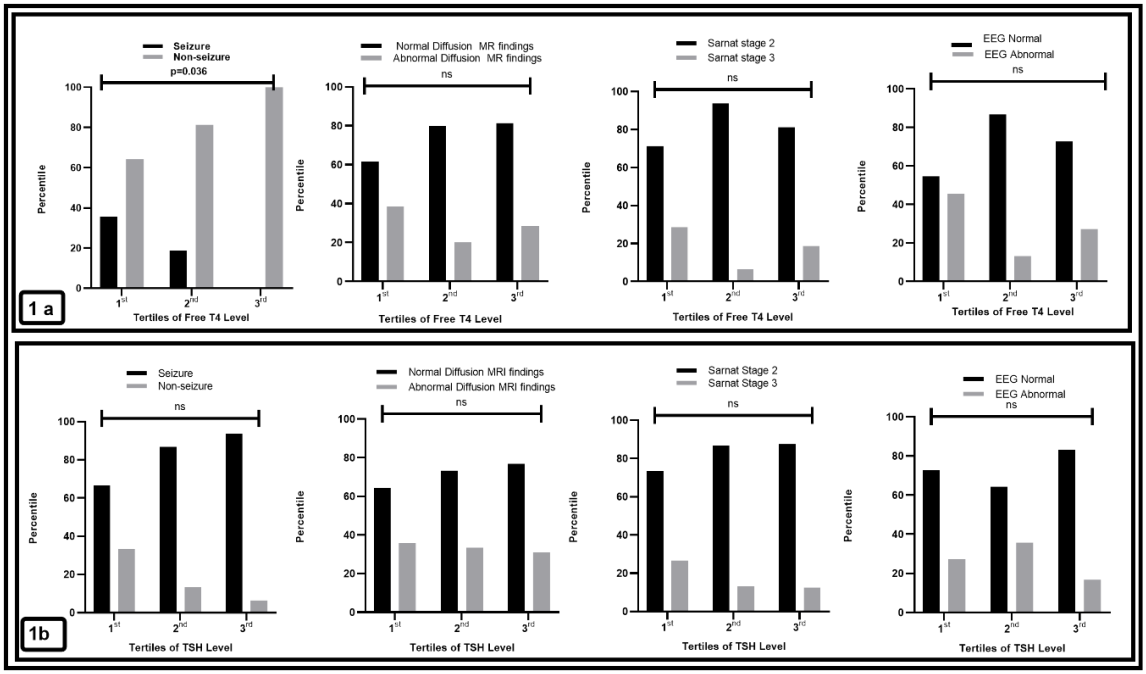

Figure 1. Magnetic resonance spectroscopy, EEG findings (normal or abnormal), Sarnat Stages (2 or 3), and the presence of seizures according to the 3 groups of fT4 (≤1.52 ng / dL, 1.52-1.84 ng /dL, and ≥1.84 ng /dL), , and TSH (≤2.56 IU / mL. 2.56-5.3 1IU / Ml, and ≥5.31 IU / mL) tertiles. **TSH**; Thyroid-stimulating hormone. **fT4;** Free thyroxine, **MRI**: Magnetic resonance imaging,

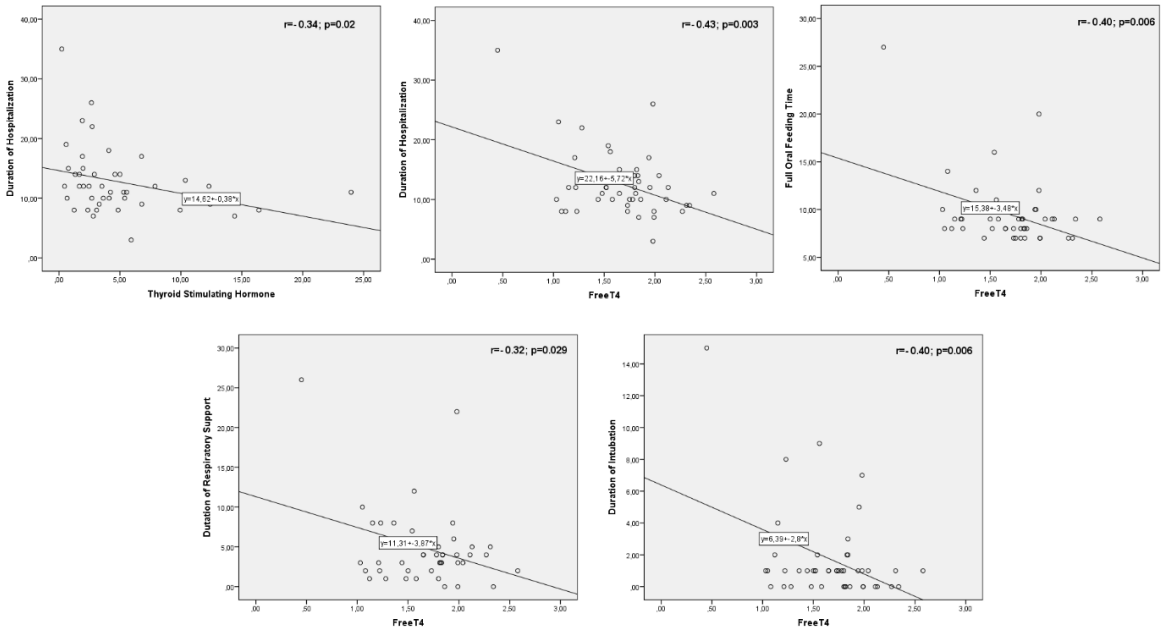

Figure 2. Correlations of fT4 and TSH levels with durations of hospitalization, respiratory support, and intubation, and time to full oral feeding. **Free T4;** Free thyroxine

Discussion

The main finding of this study was that high fT4 levels in neonates with HIE who were applied with hypothermia may be protective against neurological complications. We also found that the fT4 level was negatively correlated with length of hospital stay, duration of respiratory support, duration of intubation, and time to full oral feeding.

Perinatal asphyxia is an important cause of neonatal mortality and morbidity, and almost all organs and systems may be affected as a result of oxygen deficiency at the tissue level. Therefore, rapid deteriorations of thyroid functions have been reported in neonates in a hypoxic-ischemic state (shah et al., 2004; Hankins et al., 2002). Many studies in the literature have investigated the effect of perinatal asphyxia on thyroid functions (Borges et al., 1985; Franklin and O'Grady, 1985; Galton,1972; Moshang et al., 1980; Tahirovic , 1994; Wilson et al., 1982). It has been shown that asphyxia newborns were failed to increase ft4 levels in the first 2 days after birth (Borges et al., 1985). On the other hand, these babies have transient hypothyroxinemia (Tahirovic, 1994). Pereira et al. (Pereira and Procianoy, 2003) showed that TSH, T4, T3, and fT4 levels obtained on the first day of life in asphytic newborns (n = 17) were lower than those of the control group (n = 17). Moreover, no deaths were observed in the fT4 high (fT4>2 ng / dL) group, while mortality was seen in 6 of the 11 hypoxic-ischemic newborns with fT4 level <2.0 ng/dl. In another study, it has been shown that term newborns with low APGAR scores had lower fT4 and fT3 levels at 3, 24, and 48. hours when compared with the control group, while cord blood fT4, fT3, and TSH levels were similar. In line with these studies, the current study results also showed that low fT4 levels may be a poor prognostic marker in asphytic neonates receiving hypothermia treatment. While there was a significant relationship between ft4 level and seizures, no significant was found in babies with EEG abnormalities. This difference may be related to the fact that cases with seizures were exposed to more severe asphyxia. In contrast to the aforementioned studies, Franklin et al. (Franklin and O'Grady, 1985) showed that neonates with birth asphyxia did not have significantly different thyroid hormone levels from those of healthy control subjects. This contradictory result may be related to sampling time, the methods used to measure thyroid hormone, and a relatively small sample size.

Failure to increase fT3 and fT4 levels in a neonate with perinatal asphyxia suggests that hypoxia and/or ischemia are related to alterations in the thyroid metabolism (Borges et al., 1985). The pathogenesis of the thyroid hormone response to asphyxia in neonates is not yet fully understood. It may be related to central (hypothalamic-hypophyseal-thyroidal axis) or peripheral (tissue level) causes. Insufficient oxygenation at the tissue level in the hypothalamus and/or hypophysis, together with increased cytokines in the asphytic state, affects hypothalamic and pituitary hormone secretions (TSH, and thyroid-releasing hormone(TRH) (Ganesan and Wadud, 2020). On the other hand, cytokines may also affect the deiodinase activity at the tissue level. In an experimental study, Simonimes et al. (Simonides et al., 2008) showed that hypoxia induces hypoxia-inducible factor (HIF) expression, which causes a decrease in fT3 level to reduce the metabolic rate in hypoxic neuronal tissue, through induction of type 3 deiodinase. It may also be related to sick euthyroid syndrome (Kobayashi et al., 2018; Pereira et al., 2003). It has been shown that, neonates with perinatal asphyxia had decreased T3 levels and increased reverse T3 levels, indicating alterations in peripheral tissue (P. Et al., 2017). Low levels of thyroid hormones, as an adaptation mechanism, may also be related to reduced oxygen consumption and a lower basal metabolic rate. In many acute and chronic diseases, non-thyroidal illness syndrome is characterized by the suppression of the hypothalamus-pituitary thyroid axis and decreased thyroid hormone and TSH levels (Moura et al., 2016). Thyroid hormone levels have investigated as a prognostic factors in several studies of neonate (Das et al.,2019; Paul et al., 2010). Paul et al. (Paul et al., 2010) reported that a low fT4 level was related to the severity of respiratory disease in term neonates. In another study, Chimbo et al. (Chimbo et al., 2019) found that a low T4 level was associated with late-onset sepsis in preterm neonates. In the current study, the absence of seizures in the 3rd tertile group of fT4 (fT4>1.84

ng/dL) suggests that a higher level of fT4 may be related to a good prognostic factor in neonates with HIE. At the same time, the fT4 level was determined to be negatively correlated with duration of hospitalization, respiratory support, intubation, and time to full oral feeding.

Limitations

The study has some limitations. First, the sample size was relatively small. Second, T3, rT3, and fT3 were not measured. Third, it should be kept in mind that the thyroid hormone levels may have been affected by the inotropic agents that are frequently used in asphytic neonates. Last, because of the retrospective design, the time of the blood obtained time for measuring the thyroid hormones was not standardized (between 5-10 days), and also it may be considered as late.

CONCLUSION

In conclusion, the fT4 level may be used as a prognostic marker in neonates with HIE and seizures. Further multicenter, larger, and prospective studies are needed to support and confirm these findings.

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Conflict of Interest: The authors declare no conflicts of interest.

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