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Thyroid Function Variations in Critically Ill Neonates: A Comparative Study with Healthy Controls

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Abstract

Background: Normal thyroid function is essential for neonatal growth and brain development. In a newborn infant with severe disease, endocrine regulation of hormones can be affected by abnormal metabolism. The assessment of thyroid parameters results in the recognition of a dysfunction and its association with disease severity.
Objective: This study aimed to assess thyroid function profiles in critically ill neonates in the neonatal intensive care unit (NICU) compared with healthy controls. Additionally, we aimed to detect the presence of TD and its possible association with critical illness.
Methods: A case-control study was performed in 100 neonates, comprising 50 sick neonates and 50 healthy controls. We measured thyroid function tests (T3, FT4 and TSH) within 48 h of NICU admission and documented the absence of clinical data such as GA and BW. Statistical analysis was done by Student's t test and Mann–Whitney U test, where p 0.05).
Results: Critically ill neonates had mean T3, FT4, and TSH levels of 2.3, 1.0, and 8.7, compared with 2.5, 1.1, and 8.9 in controls. Differences were not statistically significant ($p > 0.05$).
Conclusion: The general profile of overall thyroid status was similar in the two groups but isolated cases with significantly elevated TSH encourage a close follow-up and screening.
Keywords: Thyroid, Critical, ill, Neonates.

1. Introduction

Thyroid function tests (TFTs) in the neonate are crucial for early recognition and treatment of thyroid status, which is critical to both growth and neurodevelopment. Under these conditions, critically ill neonates, including those with RDS, sepsis, or hypoxic-ischaemic encephalopathy (HIE) are particularly vulnerable. Free thyroxine (FT4) and thyroid-stimulating hormone (TSH) are generally part of TFTs. The immaturity of the hypothalamic-pituitary-thyroid (HPT) axis makes neonates, especially preterm and low birth weight (LBW) infants, vulnerable to thyroid dysfunction [1]. Transient hypothyroxinemia of prematurity (THoP) is a common condition with low serum FT4 despite normal TSH. This errant is frequently associated with reversible alterations of thyroid metabolism, which often occur in the setting of systemic illnesses, including sepsis and RDS. This situation is aggravated by the immature status of the foetal thyroid, which undergoes a sudden shift to autonomous activity at birth [1].

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The prevalence of permanent CH in preterm newborns is similar to that of term newborns, but a transient hypothyroxinemia and TSH rise delay are common. These cases are found by serial testing in neonatal screening (NBS) centres. Severely ill neonates frequently exhibit NTIS, which is manifested as low FT4 within the reference range or with low TSH. This temporary reversibility can make the diagnosis of true thyroid dysfunction difficult, especially when the situation involves sepsis or respiratory distress syndrome (RDS) or hypoxic-ischemic encephalopathy [2]. This has led to difficulty in ascertaining true thyroid dysfunction, and [3] challenges in the precision/accuracy of diagnosis. Research demonstrates that serum TSH may be increased in therapeutic hypothermia; therefore, the physicians need to scrutinize the patients again in order to avoid misdiagnosis of thyroid function simply based on HT [3]. Three. In addition, preterm SGA neonates show a higher prevalence of thyroid dysfunction and higher TSH levels as compared with AGA than need careful follow-up and potential treatment [4].

The Iraqi experience also underscores the need for routine neonatal thyroid screening. Routine screening to prevent irreversible health problems is highlighted by a study that reported significant rates of congenital hypothyroidism in Duhok [5]. This finding is consistent with the findings of a study in Sulaimani [6], which has a high rate of CH and a need for close monitoring. In critically ill neonates, the public health benefit of TFTs is to avoid irreversible neurodevelopmental damage. Early detection and treatment of thyroid problems may prevent progression to intellectual retardation and other developmental disorders [7]. To guide the management, TFTs need to be carefully interpreted considering that age-adjusted reference ranges for neonates and transient thyroid dysfunctions. True testing and interpretation are critical, as demonstrated in a study that included both Iraq [8]. The objective of the study was to determine thyroid function profiles in critically ill neonates coming to the intensive care NICU and the detection of thyroid dysfunction. In particular, the study aims to investigate potential links between thyroid dysfunction and a list of critical illnesses.

2. Method

A cross-sectional questionnaire-based study was done in the Neonatal Intensive Care Unit (NICU) of Al Mustansiriyah Academic Children's Welfare Teaching Hospital, Medical City, Baghdad, during the period from 10th June to 25th November 2024. A comparison group of healthy control were age-/sex-matched from neonates born in Baghdad Teaching Hospital within the same duration and critically ill neonates from the NICU. For consistency of comparison, 25 the gestational age and birth weights of the two groups were both restricted to 34 weeks and >2 kg, respectively. Neonates were considered critically ill if they had predefined clinical criteria such as requiring respiratory or haemodynamic support, presence of severe systemic infection, or organ dysfunction. Cases with antecedent maternal thyroid disease, congenital hypothyroidism diagnosed before admission, and incomplete medical records or insufficient blood samples were also excluded. The study protocol was approved by the institutional ethics committee and written informed consent was obtained from parents or legal guardians.

One hundred newborns were included: 50 critically sick infants and 50 controls. All demographic and clinical information was collected, such as gestational week, birth weight, maternal health during pregnancy and antenatal complications. On admission, a detailed clinical examination was carried out: vital signs and general physical examination were done; growth parameters (weight, length and

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head circumference) were compared to WHO criteria. TFT (TSH, FT4, T3) were done within 48 h of admission to NICU. When necessary, from a clinical point of view, more investigations (cerebrospinal fluid analysis, blood culture, CRP and CBC) were performed. Data were analyzed using IBM SPSS version 26. Descriptive statistics were used to summarize baseline characteristics. Categorical variables were compared between groups using chi-square or Fisher's exact tests and continuous variables t tested for normal distribution or Mann–Whitney U test where not normally distributed. Predictors of thyroid dysfunction were examined using logistic regression. A p-value less than 0.05 was considered significant as the statistical level of significance.

3. Results and discussion

Table 1 presents the demographic characteristics of both groups. The mean gestational age of neonates in the control group was 36.9 weeks (SD = 1.2), while the mean gestational age in the critically ill group was 36.8 weeks (SD = 1.1). The birth weight in both groups was similar, with the control group having a mean birth weight of 2.88 kg (SD = 0.25) and the critically ill group having a mean birth weight of 2.85 kg (SD = 0.22). sex distribution was also comparable, with 23 male and 22 female neonates in the control group, and 22 male and 23 female neonates in the critically ill group. Statistical analysis revealed no significant differences in gestational age, gender, or birth weight between the two groups ($p > 0.05$).

Table1. Demographic Characteristics of Neonates.

Parameter	Control (n=50)	Critically ill (n=50)	p-value
Gestational Age (weeks)	Mean (SD): 36.9± (1.2) 38-34	Mean (SD): 36.8± (1.1) 37-34	0.85
sex (Male/Female)	23/22	22/23	0.84
Birth Weight (kg)	Mean (SD): 2.88 ± (0.25) 3.7-2	Mean (SD): 2.85 ± (0.22) 3.5-2	0.72

The comparison of thyroid function parameters between the control and critically ill neonates revealed no statistically significant differences in the levels of triiodothyronine (T3), free thyroxine (FT4), or thyroid-stimulating hormone (TSH). The mean T3 level in the control group was 2.5 nmol/L (SD = 0.6), while the critically ill neonates had a mean T3 level of 2.3 nmol/L (SD = 0.5), with a p-value of 0.18, indicating no significant difference between the two groups Similarly, the mean FT4 level in the control group was 20 pmol/L (SD = 2.6), and the critically ill neonates had a mean FT4 level of 18 pmol/L (SD = 2.5), with a p-value of 0.27. The mean TSH level in the control group was 5.2 µIU/mL (SD = 3.0), compared to 8.7 µIU/mL (SD = 3.2) in the critically ill group, yielding a p-value of 0.72, which also showed no significant difference between the two groups. These findings suggest that thyroid hormone levels did not differ significantly between the control and critically ill neonates in this study. 4 neonates of control group have TSH more than 10 µIU/mL,two of them have TSH more than 20. 12 neonates of critical ill group have TSH more than 10 µIU/mL, six of them have TSH more than 20 µIU/mL, one of them have TSH 100 µIU/mL.; as in Table 2.

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Table2. Comparison of Thyroid Function Parameters Between Control and Critically Ill Neonates.

Parameter	Control (n = 50)	Critically Ill (n = 50)	p-value
T3 (nmol/L)	Mean ± SD: 2.5 ± 0.6 Range: 1.4–3.4	Mean ± SD: 2.3 ± 0.5 Range: 1.1–3.7	0.18
FT4 (pmol/L)	Mean ± SD: 20 ± 2.6 Range: 9.4–29	Mean ± SD: 18 ± 2.5 Range: 11.3–25.8	0.27
TSH (μIU/mL)	Mean ± SD: 5.2 ± 3.0 Range: 1.5–33.8	Mean ± SD: 8.7 ± 3.2 Range: 1.7–100	0.72

Table 3 presents the thyroid function parameters of critically ill neonates, stratified according to respiratory support status, clinical outcome, and septic screening results. Comparisons were made for mean serum levels of T3, FT4, and TSH across these subgroups. Among neonates requiring respiratory support, the mean T3 level was 2.3 nmol/L (SD 0.5), compared to 2.5 nmol/L (SD 0.6) in those not requiring support. Similarly, the mean FT4 concentration was lower in neonates receiving respiratory support (18 pmol/L, SD 2.5) than in those without support (19.5 pmol/L, SD 2.3). The mean TSH level was also marginally lower in the respiratory support group (8.5 μIU/mL, SD 3.1) compared with their counterparts (9.2 μIU/mL, SD 3.4). With respect to septic screening, neonates with positive cultures demonstrated reduced thyroid function parameters compared with those with negative results. The mean T3 level was 2.1 nmol/L (SD 0.5) in the positive group, while it was 2.6 nmol/L (SD 0.5) in the negative group. Similarly, the mean FT4 level was lower in neonates with positive cultures (16.4 pmol/L, SD 2.9) compared to those with negative cultures (18 pmol/L, SD 3.1). TSH levels followed the same pattern, with a mean of 8.8 μIU/mL (SD 3.0) in the positive group versus 9.3 μIU/mL (SD 3.3) in the negative group. Overall, neonates requiring respiratory support or with positive septic screening tended to exhibit lower levels of T3 and FT4, with slightly reduced TSH levels, suggesting a potential association between critical illness severity, sepsis, and altered thyroid function.

Table3. Thyroid Function Parameters in Critically ill Neonates**.**

Parameter	Respiratory Support (Yes) N=35	Respirator y Support (NO) N=15	Outcome (Discharged)	Culture (Positive) N=38	Culture (Negative) N=12
T3 (nmol/L)	Mean (SD): 2.3± (0.5) 1.3-4.8	Mean (SD): 2.5 ± (0.6) 1.1-3.5	Mean (SD): 4.4 ± (1.5) 1.1-4.8	Mean (SD): 2.1 ± (0.5) 1.2-3.7	Mean (SD): 2.6± (0.5) 1.5-3.5
fT4 (pmol/L)	Mean (SD): 18 ± (2.5) 23.7-12.7	Mean (SD): 19.5± (2.29) 25.8-11.8	Mean (SD): 18 ± (2.5) 29-9.4	Mean (SD): 16.4 ± (2.9) 25-10.5	Mean (SD): 18 ± (3.1) 24.1-9.4
TSH (uIU/mL)	Mean (SD): 9.2 ± (3.4) 31.5-1.5	Mean (SD): 8.5± (3.1) 22.5-1.0	Mean (SD): 8.9± (3.2) 100-0.44	Mean (SD): 9.3 ± (3.3) 31.5-0.44	Mean (SD): 8.8± (3.0) 100-0.5

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The level of thyroid function was compared between critically ill neonates and normal patients. The confounding bias is minimized due to the similar demographic variables such as age of gestation, gender and birth weight between different groups. In general, mean T3, FT4 and TSH levels were not statistically significant. Nevertheless, subgroup analysis demonstrated relevant clinical trends. T3 and FT4 were also lower in neonates on respiratory support compared to those who did not. This indicates that respiratory distress and the concomitant metabolic stress play a role in reduced production and conversion of thyroid hormones. Similar findings have been described in other studies, with reflection of hypothalamic–pituitary–thyroid axis disruption and transient hypothyroxinemia induced by critical illness [9]. Reduced thyroid function was associated with sepsis as well. T3 and FT4 values were significantly lower among the ICU neo groups compared to neonates with culture-negative. Inflammatory cytokines in sepsis may affect hormone synthesis and T4 to T3 conversion. These findings are consistent with other studies indicating hypothyroxinemia in septic neonates [10], [11]. Although the average group differences were not significant, the range of outcomes demonstrates clinically important findings.

In some neonates, the TSH was dramatically high (>20 μIU/mL), and the highest level detected in a critically ill neonate surpassed 100 μIU/mL. Such values strongly indicate hypothyroidism. These cases could be true congenital hypothyroidism rather than transient changes, and cannot be ignored as statistical outliers. This points to the need for the interpretation of group averages and individual outcomes. Analogous findings have been recorded with respect to the prevalence of congenital hypothyroidism in Iraq [5], [6], [12]. The clinical significance of these abnormalities is not yet known in the long-term perspective. Although, most neonates return to euthyroidism after resolution of the infection, short-term THV in early life could contribute to neurodevelopment. Data from congenital hypothyroidism research indicate that affected children may experience cognitive, motor and communication delays despite early treatment [13], [14]. Therefore, close surveillance and follow-up of neonates at high risk are necessary. This study has limitations. The number of patients was relatively small, which may have led to low statistical power. It is also an observational study and causality cannot be inferred from this design. Larger and multicenter studies with longitudinal follow-up are needed to clarify the impact of thyroid disease on neonatal outcome. It will be of interest in future studies to investigate the impact of severity of illness, infection and therapies such as hypothermia on control of thyroid function [3].

4. Conclusion

In this study, significant differences in thyroid function between critically sick newborns and healthy controls were not found. Even though there was no significant difference in thyroid hormone between critically ill neonates and healthy controls, further larger sample-size studies with long-term follow-up are needed for a better assessment of the influence of critical illness on thyroid function and its potential predictive value towards the outcome of neonatal lives. Further study is needed to clarify the clinical significance and long-term effects of thyroid dysfunction in neonatal patients. The goal of future studies needs to be improvement in the outcome in this very high-risk group through identification of targeted interventions, definition of the course and natural history of transient thyroid abnormalities, and refinement of neonatal screening protocols for TGS.

Conflict of Interest: There is no conflict of Interest.

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