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ORIGINAL PAPER

Evaluation of thyroid hormones and thyroid-stimulating hormone levels in critically ill full-term newborns

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ABSTRACT

Aim of the study: This study aimed to define the thyroid hormone characteristics in full-term critically ill neonates versus healthy neonates to evaluate the incidence of the euthyroid sick syndrome (ESS).

Material and methods: The present case-control study recruited 30 neonates presenting with manifestations of severe critical illness and a similar number of healthy controls. Patients were subjected to TT3, TT4, TSH, and FT4 testing.

Results: For the whole group of cases at the first sample the TT3-1 level was significantly lower than that of controls (85.63 ±33.380 ng/dl, 115.03 ±30.310 ng/dl, respectively) with a highly significant difference. The TT4-1 in cases on admission showed a highly significant difference to that of controls (7.607 ±2.2789 µg/dl, 11.219 ±2.088 µg/dl, respectively) ($p < 0.01$). TSH-1 in cases on admission was higher (6.573 ±6.6766 µIU/ml) than that of controls (3.964 ±4.5748 µIU/ml), but this did not show a significant difference ($p > 0.05$). In the second sample (5-6 days after the beginning of illness), TT3-2 (104.23 ±42.592 ng/dl) was still significantly less than that of controls (115.03 ±30.310 ng/dl), with a p-value < 0.05. TT4-2 (8.20 ±2.646), and still significantly lower than that of controls (11.219 ±2.088 µg/dl) with p-value < 0.05. TSH-2 in cases was higher (5.57 ±5.836 µIU/ml) than that of controls (3.964 ±4.5748 µIU/ml) with no significant difference ($p > 0.05$).

Conclusions: Critical illnesses are hallmarked by changes in circulating thyroid hormone parameters in full-term neonates with low TT3 concentrations in the absence of elevated TSH. The critically ill cases had a worse thyroid hormonal profile from the beginning of the disease until death compared with those who survived.

KEY WORDS:

euthyroid sick syndrome, critical illness, thyroid functions.

INTRODUCTION

Thyroid hormones are required for proper brain development throughout pregnancy and after birth. After birth, serum thyroxin (T4) and triiodothyronine (T3) levels rise dramatically, and these hormones are critical for the newborn's growth [1]. Thyroid hormone levels were observed to be abnormal in many individuals without thyroid illness. Euthyroid sick syndrome (ESS) refers to hormonal alterations in the pituitary-thyroid axis in people without thyroid disease [2, 3]. Adults after major surgery or with cardiovascular pathology or and shock have been found to have ESS [4]. There is some debate about whether these alterations represent a preventive re-

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sponse to a widespread illness or a pathologic adaptation that should be addressed.

The most common symptom of ESS is a reduction in T3 with normal levels of thyroid-stimulating hormone (TSH) and T4. ESS is divided into 2 types based on the T3 and T4 levels involved: type 1 (reduced T3) and type 2 (reduced T4) [5]. Previous research in adults found a link between illness severity and the incidence of this condition, indicating that T3 and T4 serum levels might be used as a predictive indicator [6, 7]. Furthermore, higher morbidity and death have been found in critically ill individuals with low TSH serum levels. Low T3 levels have been linked to sepsis, meningococcaemia, meningitis, bone marrow transplant, and cardiovascular surgery in children, suggesting that it might be used for prognostic purposes [5, 8, 9].

Hypothyroxinaemia has been linked to significant neurodevelopmental damage and higher perinatal death in premature infants delivered at 30 weeks of pregnancy [10]. Most clinical investigations link abnormal thyroid function to a severe disease state; however, none can entirely rule out the possibility that it is either an adaptation or a contributor to development of sickness [11, 12]. There are few studies on full-term infants, and most of them focus on the association between thyroid hormone variations and particular diseases.

This study aimed to define the thyroid hormone characteristics in full-term, critically ill neonates versus healthy neonates to evaluate the incidence of the ESS. In addition, we aimed to evaluate the relationship between thyroid hormone alternation in full-term critically ill newborns and the severity of the disease and outcome and to evaluate the thyroid profile of the survived neonates to assess if these neonates will need follow-up and/or treatment.

MATERIAL AND METHODS

The study protocol was approved by the local Ethics Committee of Abu El-Reish Hospital, Cairo University. All procedures complied with the principles of the Declaration of Helsinki and other applicable ethical statements.

STUDY DESIGN

The present case-control study recruited 30 neonates of 37 weeks or more of gestation presenting with manifestations of severe critical illness admitted to the Neonatal Intensive Care Unit (NICU) at Abu El-Reish Hospital, Cairo University. Also, 30 normal healthy neonates of matched age, sex, and weight were studied as a control group collected from the follow-up clinic. Neonates in the patients' group were included if they were full-term and had a critical illness, defined as failing vital systems that require intensive medical intervention to survive. Neonates were excluded if they were born to mothers with thyroid pathology, had confirmed hypothyroidism, neonates who were discharged or referred to other hospitals within less than 48 hours from admission, and neonates who died within the first day of admission.

TYPE OF CRITICAL ILLNESS

Neonatal infection was the main diagnosis, with 22 cases (73.3%) diagnosed with sepsis on admission. Respiratory system was the second most affected system, with 14 cases (46%) presented by respiratory distress and lung pathology. Central nervous system (CNS) affection was seen in 4 cases (13.3%). Renal affection was seen in 2 cases (6.6 %), presented mainly by oliguria and elevated kidney function tests. Cardiovascular system (CVS) affection was detected in 3 cases (10%), presented mainly by heart failure.

DATA COLLECTION AND LABORATORY TECHNIQUE

In the cases group, we collected the demographic characteristics, clinical examination findings, the assessment of the disease severity by the score for neonatal acute physiology (SNAP score) [13], needs for mechanical ventilation, laboratory investigations findings, and outcomes. In the control group, demographic characteristics and the results of the thyroid function test were collected.

The samples for thyroid function tests for the case group were collected within 24-48 hours from critical illness, 5-6 days later, and immediately before discharge or death. The performed tests included TT3, TT4, TSH, and FT4, which was taken in improved cases only to detect if the patient required follow-up or treatment. Two millilitres of blood were obtained from each neonate. The assessment of TT3, TT4, TSH, and FT4 was done using a RIAKEY T3/T4 RIA Tube (Shinjin Medics inc., Korea).

MANAGEMENT OF PATIENTS WITH THYROID DYSFUNCTION

Neonates with thyroid dysfunction were managed according to the guidelines of the American Academy of Pediatrics (2006).

STATISTICAL ANALYSIS

Continuous data with normal and abnormal distribution were expressed as mean (±SD) and median (interquartile range [IQR]) values, respectively. Categorical data were expressed as a count and percentage. Data were compared using Student's *t*-test, one-way ANOVA test, and χ^2 test according to the data type. A probability value (*p*-value) less than 0.05 was considered statistically significant.

RESULTS

Of our 30 critically ill cases, there were 14 males (46%), with a male-female ratio of 7 : 8. While in the control group, males amounted to 18 (56.3%), with a male-

TABLE 1. Descriptive data of cases and controls

Factor	Cases ($n = 30$)		Controls ($n = 30$)		p-value	Significance
	n	%	*n*	%		
Sex						
Male	14	46.7	18	56.3	0.450	NS
Female	16	53.3	14	43.8		
Gestational age (week)						
Mean ±SD	38.03 ±0.964		38.09 ±0.963		0.777	NS
Weight [g]						
Mean ±SD	2760.00 ±533.208		2900.00 ±607.179		0.278	NS
Age on first measurement (days)						
Mean ±SD	9.73 ±8.642		5.73 ±3.642		0.827	NS

NS – non-significant, SD – standard deviation

female ratio of 6 : 7. There was no significant difference between cases and controls regarding sex ($p > 0.05$). The mean gestational age of the cases was 38.03 ±0.964 weeks and in controls it was 38.09 ±0.96 weeks. The mean of weight was 2760 ±533.20 g in cases and 2900 ±607.17 g in controls. The mean of age of cases on admission was 9.73 ±8.64 days, while in controls the mean of age at hormone measurement was 5.73 ±3.64 days. There was no significant difference between cases and controls regarding gestational age, weight, and age at first measurement ($p > 0.05$, Table 1).

Seventeen cases out of 30 (56.7%) required mechanical ventilation support immediately after admission into the NICU, and 13 cases (43.3%) required from nasal oxygen to box oxygen support. The mean of number of failed systems on admission was 2.07 ±0.890. Multi-organ system failure (MOSF) was observed in 8 (26%) cases.

Clinical and laboratory data were collected during the first 24 hours of admission after start of illness and according to the SNAP score items as shown in Table 2. The mean systolic blood pressure (71.53 ±12.931 mm Hg), the mean RR (60.87 ±9.885 mm Hg), the increased I : T ratio (0.3040 ±0.16947), and blood glucose level (176.13 ±82.058) indicated the severity of illness in these cases on admission. The mean temperature (36.220 ±0.8040°C), and the mean of pH (7.2273 ±0.12289) were lower, indicating the severity of illness in these cases on admission. The severity of the disease in cases was evaluated by SNAP score on admission; its mean was 16.93 ±5.64 at the first measurement of thyroid hormones and TSH on admission at the beginning of the disease.

For the whole group of cases at the first sample the TT3-1 level in cases was significantly lower than that of controls (85.63 ±33.380 ng/dl, 115.03 ±30.310 ng/dl, respectively) with a highly significant difference. The TT4-1 in cases on admission showed a highly significant difference with that of controls (7.607 ±2.2789 µg/dl, 11.219 ±2.088 µg/dl, respectively) ($p < 0.01$). TSH-1 in cases on admission (6.573 ±6.6766 µIU/ml) was higher than that of controls (3.964 ±4.5748 µIU/ml), but this did not show a significant difference ($p > 0.05$). In the second sample (5-6 after post the beginning of illness) TT3-2 (104.23 ±42.592 ng/dl) was still significantly less than that of controls (115.03 ±30.310 ng/dl) with a p-value < 0.05. TT4-2

TABLE 2. Baseline clinical and laboratory characteristics of the studied cases according to score for neonatal acute physiology items on admission

Character	Mean ±SD	Range	Median
Highest MBP [mm Hg]	71.53 ±12.931	45–100	70
Lowest MBP [mm Hg]	41.87 ±11.557	25–61	40
Highest HR [BPM]	167.90 ±14.646	135–198	166
Lowest HR [BPM]	111.87 ±14.682	83–140	112
RR [BPM]	60.87 ±9.885	40–80	64
Temperature [°C]	36.22 ± 0.804	34–37.5	36
UOP [cc/kg/h]	1.75 ±0.515	1–2.5	1.9
pH	7.23 ±0.123	7–7.6	7.2
Highest HCO_3 [mmol/l]	20.76 ±5.021	13–34	20
Lowest HCO_3 [mmol/l]	13.46 ±4.083	3–20	14
BUN [mg/dl]	37.20 ±21.755	7–100	40
Creatinine [mg/dl]	0.88 ±1.129	0.1–6	0.8
Highest Na [mEq/l]	143.57 ±12.705	125–180	140
Lowest Na [mEq/l]	132.53 ±9.362	116–145	133
Highest K [mEq/l]	5.68 ±1.061	3.4–7.9	5.4
Lowest K [mEq/l]	4.30 ±1.056	3–6	4
Highest HCT	39.42 ±9.785	20–50	30
Lowest HCT	29.85 ±8.975	13–40	20
TLC [$\times 10^3/mm^3$]	10.61 ±4.578	3–22	10
I : T	0.30 ±0.169	0.06–0.6	0.26
PLT [$\times 10^9$/l]	206.07 ±104.874	33–451	198
Highest BG [mg/dl]	176.13 ±82.058	67–456	157
Lowest BG [mg/dl]	102.30 ±5 8.340	38–250	85
SNAP	16.93 ±5.640	7–30	–

BG – blood glucose, BUN – blood urea nitrogen, HCT – hematocrit, HR – heart rate, MBP – mean blood pressure, PLT – platelets, RR – respiratory rate, SNAP – score for neonatal acute physiology, TLC – total lymphocyte count, UOP – urine output

TABLE 3. Monitoring of thyroid hormones and thyroid-stimulating hormone values in cases during hospital stay versus controls

	Cases	Controls	*p*-value	Significance
TT3 [ng/dl]				
TT3-1	85.63 ±33.38	115.03 ±30.310	0.001	HS
TT3-2	104.23 ±42.59		0.035	S
TT3-3	109.07 ±35.17		0.463	NS
TT4 [µg/dl]				
TT4-1	7.61 ±2.270	11.22 ±2.088	0.000	HS
TT4-2	8.20 ±2.646		0.034	S
TT4-3	8.04 ±2.190		0.048	S
TSH [µIU/ml]				
TSH-1	6.57 ±6.670	3.96 ±4.575	0. 347	NS
TSH-2	5.57 ±5.836		0.217	NS
TSH-3	5.77 ±5.070		0.065	NS

HS – highly significant, NS – non-significant , S – significant

(8.20 ±2.646) was still significantly lower than that of controls (11.219 ±2.088 µg/dl) with p-value < 0.05. TSH-2 in cases (5.57 ±5.836 µIU/ml) was higher than that of controls (3.964 ±4.5748 µIU/ml) with no significant difference (p > 0.05). Samples taken before discharge or death show that TT3-3 levels were still lower (109.07 ±35.172 ng/dl) than the TT3 in the controls (115.03 ±30.310 ng/dl) but without significant difference (p-value > 0.05). As regards TT4-3 in cases, it was (8.04 ±2.190 µg/dl) still significantly lower than that of controls (11.219 ±2.088 µg/dl) with p-value < 0.05. TSH-3 was still higher (5.770 ± 5.0771 µIU/ml) than that of controls (3.964 ±4.5748 µIU/ml) but without significant difference (p > 0.05) (Table 3).

DISCUSSION

In the current study, neonatal infections were the main pathology of most admitted cases, followed by respiratory, neurological, renal, and cardiac diseases. The mean number of failed systems on admission was 2.07 ±0.890. MOSF was observed in 8 (26%) cases. Goldsmit *et al.* studied 94 neonates to describe the thyroid hormone profile in critically ill full-term newborns versus healthy infants. They reported that the failure of one organ was recorded in 41% of the studied neonates, whereas failure in two or more organs was present in 19% of the studied neonates [14].

On admission, the disease severity was evaluated by the SNAP score, with a mean of 16.93 ±5.64. This score was used in many studies to assess severity. A retrospective study by Vasudevan *et al*. stated that SNAP correlates well with mortality in neonates admitted to the Paediatric Intensive Care Unit (PICU) [15]. Goldsmit *et al.* also used the SNAP score to assess disease severity and investigate its correlation to thyroid hormones [14]. Sutton *et al*. described the use of this score as a measure of illness severity in mechanically ventilated term infants. They found that the highest mean of SNAP scores was observed in ventilated infants with meconium aspiration and perinatal asphyxia, compared with pulmonary hypertension and respiratory distress syndrome. They also highlighted that SNAP is a valuable measure of severity of illness in sick term neonates admitted to the Neonatal Intensive Care Unit (NICU) [16].

Regarding the thyroid hormone profile, we found that the diseased neonates had significantly lower TT3 and TT4 levels compared with controls. On the other hand, there was no significant difference between the groups in terms of TSH. Goldsmit *et al.* [14] showed a highly significant difference between cases and controls in both TT3 and TT4 (p < 0.01). Similarly to us, they found that TSH in cases was comparable to that of controls. Lim *et al.* found similar results, but their study was restricted to term newborns on mechanical ventilator support during the first week of life [17]. Paul *et al.* investigated 20 full-term neonates who required mechanical ventilation or nasal continuous positive airway pressure. The study showed that thyroid hormones and TSH were significantly decreased in those neonates and correlated inversely with the SNAP score [18]. As regards TSH level, other studies found different results; some neonates with critical illness had transient elevations in serum TSH concentrations (up to 20 mU/l) during recovery from nonthyroidal illness syndrome (NTIS) compared with healthy neonates [19, 20]. This was explained by Hemmati and Pishva [20] and Larson *et al.* [21], who stated that the spectrum of thyroid function abnormalities in critically ill neonates includes many pictures; one of them was transient primary hypothyroidism with a late rise of TSH. This pattern can be confusing if the elevated TSH level is associated with the still reduced concentration of FT4. Such patients meet all laboratory criteria for primary hypothyroidism except for the clinical content. The follow-up generally reveals a normalization of TSH and T4 within 1-2 months [20]. Goldsmit *et al.* proved that TSH could be low but only in a prolonged

illness. They found that only 9% of cases showed decreased TSH, TT3, and TT4, with high mortality risk [14]. These changes were documented in many other studies and are collectively referred to as ESS or (NTIS) [22].

Our findings showed that there is no significant correlation between the TT3 and TT4 levels and gender, age, or weight, among the cases. A significant negative correlation was observed between TT3 and TT4 levels and MOSF. In addition, TT3 and TT4 had a significant negative correlation with the SNAP score. In agreement with this, Suvarna and Fande's study reported the same for sex, weight, and age and added the duration of hospital stay because all these factors failed to show any effect or correlation with the patient thyroid hormone profile [23]. The relationship between neonatal pathology and thyroid hormone levels has been previously discussed in many studies, especially in cardiovascular pathology, which have reported the association of low thyroid hormones and cardiac affection in newborns [24, 25]. This concurs with the study of Goldsmit *et al.*, i.e. no differences were found in the initial TT3 and TT4 values according to the type of pathology on admission, but a significant negative correlation was found with MOSF ($p < 0.05$). In addition, they found a highly significant correlation between SNAP score and both TT3 and TT4 (TT3: $r = -0.27$, $p = 0.008$) (TT4: $r = -0.40$, $p = 0.001$) [14]. Similar data were mentioned by Shih and Agus, who stated that the decreased TT3 hormone levels were also significantly associated with increased organ failure, which was commonly seen in cases with sepsis [22]. This was explained by the fact that patients with systemic inflammatory response syndrome (SIRS) have increased leukocyte counts, oxidative stress, and release of cytokines, which probably contribute to NTIS development [26].

By monitoring thyroid hormones and TSH levels after 5-6 days of critical illness beginning with a second measurement, 56.6% of all cases had low TT3, and 43.3% of all cases continued with low TT3 and TT4 hormones; TSH levels were not affected. Furthermore, the low TT3 and TT4 group had a higher SNAP score on admission than the low TT3 group. Goldsmit *et al.* found that, in the most severely ill patients (high SNAP scores), low TT3 was associated with low TT4 [14]. This was also mentioned in the review article by Shih and Agus, who stated that low serum TT4 correlates with severe illness and poorer prognosis [22]. They explain this by low TRH – due to neuroendocrine changes that occur with increased severity or chronicity – causing low TSH, which results in low thyroidal secretion and reduced serum concentrations of the thyroid-hormone binding proteins, a major cause of low TT4 in NTIS. The increased free fraction of T4 causes feedback suppression of TSH and decreased thyroidal secretion.

Out of 30 studied neonates, 40% died and 60% improved. Of all the cases who died, 33.4% were from the low TT3 group and 66.6% were from the low TT3 and TT4 group. The SNAP score on admission in the cases who died was significantly more elevated than the SNAP score in the improved cases ($p < 0.01$). The sensitivity and specificity of the SNAP score in predicting death was 100% at cut-off level [28]. The study of Lim *et al.* revealed an association between decreased TT4 and outcome in term infants with respiratory distress. Goldsmit *et al.* found the same results in their study and added that cases who died with lower thyroid hormones also had a high SNAP score, longer stay in the NICU, more days on a ventilator, and a greater need for rescue therapies than the improved group [14]. Dehghani *et al.* stated that patients with decreased TT4 levels need a liver transplant sooner than those patients who do not have decreased TT4 levels [27]. Meyer *et al.* found that thyroid hormones were lower in cases who died than in improved cases and therefore stated that such a profile on admission could be used as an adverse prognostic marker directly related to disease severity and poor outcome in infants [28]. Angelousi *et al.* agreed, and mentioned that the association between lower TT3 or TT4 and worse outcome of patients could be of prognostic value [26].

In this study, a sample of FT4 was taken from the improved cases before discharge; it was lower than that of controls with a significant difference ($p < 0.01$). By correlating this FT4 to the thyroid hormones and TSH in the first measurement on admission in these improved cases, there was a significant positive correlation with TT3 and TT4. These correlations could be helpful in predicting patients with low FT4 before discharge who may later need treatment.

Finally, we highly recommend that thyroid function tests are interpreted with caution in neonates with NTIS. Critical analysis of the pattern of thyroid function tests (including TSH, total and free thyroid hormone levels) is necessary for a correct interpretation. Monitor thyroid function tests in the improved neonates at and post-discharge to assess if they will need treatment in the future.

A recent review of LaFranchi *et al.* [29] suggested a benefit of thyroid replacement in low-birth neonates. However, a large-scale study is required to determine if there is any benefit from early hormonal replacement therapies.

CONCLUSIONS

Critical illnesses are hallmarked by changes in circulating thyroid hormone parameters in full-term neonates with low TT3 concentrations in the absence of elevated TSH. The critically ill cases had a worse thyroid hormonal profile from the beginning of the disease until death compared with the ones who survived. The group with low levels of both TT3 and TT4 had the worst hormonal profile and a higher SNAP score than the group with low TT3 alone. TT3 and TT4 levels on admission could be added to the SNAP score to enforce its prognostic value in predicting outcomes.

DISCLOSURE

The authors declare no conflict of interest.

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