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Frequency of non-thyroidal illness syndrome in pediatric patients with sepsis and septic shock

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Abstract

Background: Non-thyroidal illness syndrome (NTIS) is considered when patients demonstrate altered thyroid hormones and is frequently seen in patients with sepsis and septic shock. Levels keep affected with disease progression and usually get normalized after the sickness is cured. NTIS is not studied well in pediatric population.

Aim of the work: Our primary outcome was to assess the frequency of hormonal changes of NTIS in sepsis and septic shock patients. The secondary outcome was to follow-up the severity of NTIS and its effect on the prognosis of the primary illness.

Patients and methods: This study (1st phase: cross-sectional, 2nd phase: prospective) included 40 critically ill children categorized into two groups: (i) sepsis group: defined according to standard international criteria using pediatric Sequential Organ Failure Assessment (p SOFA) score and sepsis was considered when p SOFA score > 2; (ii) septic shock group: defined by a vasopressor requirement to maintain a mean arterial pressure ≥ 65 mmHg and having a serum lactate level > 2 mmol/L despite adequate fluid resuscitation, with 20 patients in each group. Patients were admitted to the pediatric intensive care unit (PICU). Thyroid hormone levels were assessed and compared in day 1 and day 5 in all patients and subgroups. All patients were followed up until discharge or death.

Results: NTIS was found in 47.5% of patients. NTIS was higher among septic shock group than sepsis 65.5% versus 30% ($p = 0.027$). NTIS was associated with each of ventilation, catecholamines infusion and SOFA score ($p = 0.044$, 0.027, and 0.033) respectively. FT3 (free triiodothyronine) levels were lower and rT3 (reverse T3) levels were higher in day 5 of sickness than day 1 ($p = 0.041$ and 0.000) respectively. Furthermore, FT3 levels in day 5 were lower, and rT3 levels in day 1 and day 5 were higher in non-survivors than survivors ($p = 0.002$, 0.015, and 0.003) respectively. ROC curve was done to assess predictors of mortality and revealed that FT3 levels in day 5 was the best in predicting PICU mortality, followed by SOFA score day 5.

Conclusion: NTIS is common among critically ill children and higher among septic shock group than sepsis. Also, beside the SOFA score, FT3 measured in day 5 of sickness were the best predictors of PICU mortality.

Keywords: Sepsis, Septic shock, Sickness, Thyroid hormone levels, Non-thyroidal illness syndrome

Background

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection and "septic shock"; the subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality [1]. Determination of an acute prognosis

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in the early stage of sepsis and septic shock is of great importance to aid in the development of adapted strategies and improve patient outcomes. Several prognostic biochemical and clinical scoring systems were developed to assess the morbidity and mortality in septic shock, but none is standarized [2]. Thus, new biomarkers for reliable early prognosis are still needed. Pediatric Patients suffering from critical sicknesses who require treatment in pediatric intensive care unit (PICU) present with alterations in circulating thyroid hormone levels that are referred to with several names such as non-thyroidal illness syndrome (NTIS), euthyroid sick syndrome (ESS) also known as the low T3 syndrome. NTIS demonstrate altered thyroid functions (low serum FT3 and TT3, normal or mildly increased FT4 and TT4, and normal or low TSH concentrations. In severe cases, the TT4 and FT4 concentrations might be low and that of TSH normal) [3, 4]. NTIS could be attributed to increased deiodination of thyroxine (T4) to reverse T3 (rT3), rather than T3 and increased catabolism of T3 to 3,3-diiodothyronine (T2) [5]. However, rT3 elevation is not a must; where serum rT3 may be low, normal, or high as production of rT3 is sometimes restricted by the low level of substrate (T4) in serum and in tissues and probably by inhibited T4 influx into cells [6].

Such changes of the serum thyroidal hormones differ from those in primary or secondary thyroid disorders and refer to distortions in thyroid functions without thyroid disease [7]. This syndrome is associated with adverse outcomes in many diseases, including infectious diseases [8], cardiovascular [9], gastrointestinal diseases [10], trauma [11], and unselected critical sickness patients [12]. Although the severity of sickness strongly correlates with the severity of the NTIS phenotype, the causality of this association remains departed, and pathophysiological mechanisms remain incompletely understood. Thyroid dysfunction has also been found to be associated with the mortality of patients admitted to the PICU [13]. Researchers in some studies demonstrated that free triiodothyronine (FT3) levels in non-survivors were significantly lower than those in survivors [14], While others found that determining rT3 levels may be a helpful test to identify an increased risk for PICU mortality in critically ill patients [15]. Other researchers showed that there was no association between FT3 levels and ICU patient outcomes [16]. Conflicting results also were reported in terms of other indicators, such as FT4 and TSH [17].

Methods

Patients

Study type and setting

This study (1st phase: cross-sectional study, 2nd phase: prospective study) was conducted at pediatric intensive care unit (PICU), Children's Hospital, Ain Shams University, Cairo, Egypt.

Target population

A total of 40 patients aged 6 months to 10 years old, who were admitted in PICU, Children's Hospital, Ain Shams University, were recruited over the period from June 2021 to December 2021. Patients were categorized into two groups: sepsis group and septic shock with 20 patients in each group were followed up until discharge or death. Finally, the patients were again divided into two groups according to outcome: survivors and non-survivors.

All studied pediatric patients were recruited sequentially according to the following selection criteria

Inclusion criteria

Age group: Between 6 months–10 years.

Gender: Both males and females.

Septic patients

Sepsis was defined according to standard international criteria using pediatric Sequential Organ Failure Assessment (pSOFA) score and sepsis was considered when pSOFA score > 2 [18].

Septic shock was defined by a vasopressor requirement to maintain a mean arterial pressure $\geq$ 65 mmHg and having a serum lactate level > 2 mmol/L despite adequate fluid resuscitation [18].

We defined NTIS according to Journal of the Endocrine Society as reduced serum T3 levels without concomitant rise in TSH (low or normal TSH) with or without other thyroid hormonal changes [3, 4].

Exclusion criteria

1. Patients having thyrotoxicosis/hypothyroidism before admission to PICU.
2. Patients with previous liver or renal disease before the onset of shock.
3. Patients with brain injury.
4. Patients taking drugs that affect thyroid functions.
5. Patients with NTIS receiving thyroid replacement therapy.
6. Malnourished patients (children were classified as being wasted or underweight according to the WHO [19].

Methodology

Data collection

a. Full medical history including personal history (age and sex), history of present illness, past history of

medical importance, long of stay in PICU, duration of mechanical ventilation**.**

b. Through clinical examination:

- *Anthropometric measurements*: weight (kg) and length or height (cm).
- Vital data monitoring including heart rate, non-invasive blood pressure monitoring, skin and core temperature, transcutaneous oxygen saturation.
- Ventilatory support and its setting in mechanically ventilated patients.

Measurements

Assessment of thyroid hormone levels (FT3, FT4, TSH, and rT3) through blood samples (1 cm) were collected by venipuncture and analyzed using EIA kits based on enzyme-linked immunosorbent assay (ELISA) technique and performed in Clinical Pathology Department, in Children's Hospital, Ain Shams University.

According to EIA kits that we used; the normal ranges of serum thyroid hormone concentrations were as follows: FT3 = 2.15–4.88 pg/ml, FT4 = 0.893–1.89 ng/dL, TSH = 0.260–4.2 μIU/mL, rT3 = 6.9–26.2 ng/dl.

A complete diagnostic workup was performed in all patients, including:

1. Complete blood count (CBC)
2. C-reactive protein (CRP)
3. Venous blood gases (VBG)
4. Kidney functions: urea and create
5. Liver functions: alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, total bilirubin, and direct bilirubin
6. Blood culture

Blood samples were collected from each participant on the day 1 and day 5 of sickness for FT3, FT4, TSH, rT3, CBC, and CRP.

1. *Scoring systems*: pediatrics sequential organ failure assessment (pSOFA) scores were calculated on studied patients in day1 and day 5 of sickness [20].

Statistical analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when parametric and median, inter-quartile range (IQR) when data found non-parametric. Also, qualitative variables were presented as number and percentages.

The comparison between groups regarding qualitative data was done by using *chi-square test* and/or *Fisher's exact test* when the expected count in any cell found less than 5.

The comparison between two independent groups with quantitative data and parametric distribution was done by using *independent t test* while with non-parametric distribution were done by using *Mann-Whitney test.*

Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group.

Receiver operating characteristic curve (ROC) was used to assess the best cut off point with its sensitivity, specificity, positive predictive value, negative predictive value, and area under curve (AUC) of the studied marker.

Results

A total of eighty patients, meeting the inclusion criteria, were prospectively studied. Among them 23 were males (57.5%) and 17 were females (42.5%). The mean age of the patients was 26.45, ranging 6–120 months. Ventilated patients were 30 and the median days of ventilation was 5.5 (4–12) days. Median days of stay in PICU was 10 (5.5–15) days.

Thyroid hormone levels in day 1 of sickness

FT3 levels within the normal range of 2.15–4.88 pg/ml was found in 21 patients (52.5%), while the other 19 patients (47.5%) had a FT3 levels below the lower reference range.

FT4 levels within the normal reference range of 0.893–1.89 ng/dl was found in 23 patients (57.5%), while 17 patients (42.5%) had FT4 levels below the lower reference range. TSH levels within the normal reference range (0.26–4.2 uIU/ml) was found in 15 patients (37.5%), while 25 patients (62.5%) had TSH levels below the lower reference range. rT3 levels higher than the normal reference range of (6.9–26.2 ng/dl) was found in all patients (100%).

In day 5 of sickness FT3, FT4, and TSH levels below the reference range were found in 56.7%, 26.7%, and 66.7% of patients respectively, while rT3 levels was found to be higher than the normal range in 40 patients (100%). FT3 levels were lower while rT3 levels were higher in day 5 of sickness than day 1 ($p = 0.041$ and $p = 0.00$) respectively (Table 1).

NTIS in septic shock groups compared sepsis

NTIS was found in 47.5% of total patients who had reduced serum T3 levels without concomitant rise in TSH levels (low or normal TSH) with or without

Table 1 Comparison between D 1 and D 5 regarding thyroid hormone levels

		Day 1 No. = 40	Day 5 No. = 30	Test value	*P* value
FT3 (pg/ml)	Median (IQR)	2.53 (1.94–3.91)	1.87 (1.37–3.91)	− 2.047≠	0.041
	Range	1.02–4.88	0.52–5.21		
	Low	19 (47.5%)	17 (56.7%)	2.182	0.336
	Normal	21 (52.5%)	12 (40.0%)		
	High	0 (0.0%)	1 (3.3%)		
FT4 (ng/dl)	Median (IQR)	1.15 (0.76–1.4)	1.32 (0.85–1.48)	− 1.029≠	0.304
	Range	0.08–1.83	0.31–1.94		
	Low	17 (42.5%)	8 (26.7%)	2.963	0.227
	Normal	23 (57.5%)	21 (70.0%)		
	High	0 (0.0%)	1 (3.3%)		
TSH (μIU/mL)	Median (IQR)	0.2 (0.1–0.8)	0.2 (0.1–0.8)	− 0.282≠	0.778
	Range	0.1–4	0.1–3.5		
	Low	25 (62.5%)	20 (66.7%)	0.130	0.937
	Normal	15 (37.5%)	10 (33.3%)		
	High	0 (0.0%)	0 (0.0%)		
rT3 (ng/dl)	Median (IQR)	155 (75–215)	260 (160–340)	− 3.542≠	0.000
	Range	50–445	60–520		

FT3 free triiodothyronine, *FT4* free thyroxine, *TSH* thyroid stimulating hormone, *rT3* reverse T3

Table 2 Descriptive characteristics of studied patients regarding NTIS frequency

NTIS	Sepsis group No. = 20	Septic shock group No. = 20	All cases No. = 40	Test value	*P* value
NTIS	6 (30.0%)	13 (65.0%)	19 (47.5%)	4.912	0.027

NTIS non-thyroidal illness syndrome

Table 3 Comparison between sepsis and septic shock regarding the thyroid hormones in day 5

		Sepsis group No. = 20	Septic shock group No. = 20	Test value	*P* value
FT3 (pg/ml) in day 5	Median (IQR)	3.26 (1.48–3.91)	1.56 (1.34–1.91)	− 2.054≠	0.040
	Range	1.02–4.88	0.52–5.21		
rT3 (ng/dl) in day 5	Median (IQR)	160 (90–260)	340 (280–380)	− 3.393≠	0.001
	Range	60–460	200–520		

FT3 free triiodothyronine, *rT3* reverse T3

Table 4 Comparison between sepsis and septic shock regarding the thyroid hormones in day 1 of illness

		Sepsis group No. = 20	Septic shock group No. = 20	Test value	*P* value
FT4 (ng/dl) in day 1	Median (IQR)	1.32 (1.03–1.55)	0.78 (0.68–1.17)	− 2.453≠	0.014
	Range	0.08–1.79	0.54–1.83		
	Range	0.31–1.85	0.47–1.94		

FT4 free thyroxine

Table 5 NTIS among survivors and non survivors

	Survivors No. = 19	Non-survivors No. = 21	All cases No. = 40	Test value	*P* value
NTIS	6 (31.6%)	13 (61.9%)	19 (47.5%)	3.679	0.055

NTIS Non-Thyroidal Illness Syndrome

5 were lower and rT3 levels were higher in patients with septic shock as compared to patients with sepsis; 1.56 (1.34–1.91 pg/ml) versus 3.26 (1.48–3.91 pg/ml) and 340 (280–380 ng/dl) versus 160 (90–260 ng/dl) with the following p values ($p = 0.04$) and ($p = 0.014$) respectively (Tables 3 and 4).

Table 6 Comparison between survivors and non-survivors regarding the thyroid hormone levels in day 1 and day 5

		Survivors No. = 19	Non-survivors No. = 21	Test value	*P* value
FT3 (pg/ml) In day 5	Median (IQR)	3.26 (1.56–4.04)	1.43 (1.17–1.82)	− 3.125≠	0.002
	Range	1.17–5.21	0.52–2.08		
rT3 (ng/dl) In day 1	Median (IQR)	90 (70–190)	200 (110–270)	− 2.439≠	0.015
	Range	50–280	70–445		
rT3 (ng/dl) In day 5	Median (IQR)	200 (90–270)	340 (280–395)	− 3.015≠	0.003
	Range	60–440	180–520		

FT3 Free triiodothyronine, *rT3* reverse T3

Table 7 Correlations between FT3 in day 5 of illness regards days of ventilation, days of stay in PICU, SOFA score, CRP

Non-survival	FT3 (Pg/ml)	
	R	*P* value
Days of ventilation	− 0.966	0.000
Stay in PICU (Days)	− 0.745	0.009
SOFA score	− 0.926	0.000
CRP	− 0.700	0.016

FT3 free triiodothyronine, *CRP* C-reactive protein, *SOFA score* Sequential Organ Failure Assessment score

PICU mortality

The patients were followed up until discharge or death and based on the outcome, they were divided into two groups: survivors (included 19 patients) and non-survivors (included 21 patients). NTIS was found to be more prevalent among non-survivors compared to survivors (61.9% versus 31.6%); however, the values did not reach level of significance (Table 5).

FT3 levels in day 5 among non-survivors were significantly lower than survivors ($P = 0.002$). rT3 levels in days 1 and 5 were higher among non-survivors ($P = 0.003$) (Table 6).

Table 8 Value of indicators in predicting PICU mortality

	Cut-off point	AUC	Sensitivity	Specificity	+PV	− PV
rT3 (ng/dl) day 1	> 200	0.724	47.62	94.74	90.9	62.1
SOFA score day 1	> 6	0.779	76.19	68.42	72.7	72.2
FT3 (pg/ml) day 5	≤ 2.08	0.847	100.00	68.42	64.7	100.0
rT3 (ng/dl) day 5	> 270	0.835	81.82	78.95	69.2	88.2
CRP day 5	> 57	0.751	81.82	68.42	60.0	86.7
SOFA score day 5	> 3	0.837	100.00	57.89	57.9	100.0

The cut-off value of FT3 in day 5 was ≤ 2.08 Pg/ml which gives sensitivity 100% and specificity 68.42%. And show the cut-off value of SOFA score day 5 was > 3 which gives sensitivity 100% and specificity 57.49%

rT3 reverse T3, *FT3* free triiodothyronine, *CRP* C-reactive protein, *SOFA score* Sequential Organ Failure Assessment score

other thyroid hormonal changes. NTIS was significant in septic shock groups compared to sepsis 65% versus 30% ($p = 0.027$) (Table 2). FT4 levels in day 1 were lower in patients with septic shock as compared to patients with sepsis 0.78 (0.68–1.17 ng/dl) versus 1.32 (1.03–1.55 ng/dl) ($p = 0.014$). FT3 levels in day

Correlation between FT3 on day 5 with other parameters within non-survivors

We found significant negative correlations between FT3 in day 5 and each of days of stay in PICU, days of ventilation, SOFA score, and CRP); ($P = 0.000$, 0.009, 0.000, and 0.016 respectively) (Table 7).

Receiver operating characteristic (ROC) curves were constructed to examine the performance of indicators as predictors of PICU mortality; the area under the curve (AUC) for each indicator was calculated. FT3 levels in day 5 with largest AUC (0.847) was the best in predicting PICU mortality (sensitivity 100%, and specificity 68.42%), followed by SOFA score day 5 (AUC = 0.837, sensitivity 100%, and specificity 57.89%) (Table 8).

Discussion

Thyroid hormone changes appear in patients with serious sickness such as sepsis and septic shock as a favorable adaptation response of metabolic functions to stress and critical sickness [21]. Forty patients were included in our study. NTIS was found in 19 patients (47.5%). Our results were comparable to those obtained by El-Ella et al. 2019 and Hu et al. 2015 who found that 63% and 57% respectively of critically ill children had NTIS [22, 23]. Similarly in neonates, NTIS was diagnosed in 60.7% of full term neonates with sepsis [24]. On the other hand, previous studies showed that all children with meningococcal sepsis and/or undergoing cardiac bypass surgery had NTIS [25, 26]. This wide variability could be explained by differences between the studies in terms of age of studied patients, underlying critical sickness, sample size, assay technique, or other factors like ethnicity or salt iodination. Moreover, medications widely used in PICU could be incriminated. We found that NTIS frequency in septic shock group was nearly double that of the sepsis (65% versus 30%) which was in accordance with results obtained by previous studies that reported thyroid hormone levels were significantly lower in children with septic shock, compared to sepsis [27–29]. Also, NTIS was more prevalent among non-survivors than survivors; however, the values did not reach level of significance. Moreover, literature showed that NTIS was significantly correlated with the severity of the disease, and the decline in FT3 levels is used to evaluate mortality [13].

As regards NTIS and FT3 levels' correlations with stay in PICU, ventilation, catecholamines infusion, SOFA score, and CRP, we observed that

- ❖ FT3 levels were negatively correlated with each of duration of stay in PICU and ventilation

Our findings were consistent with the study by Marks et al. 2009 who reported that lower T3 levels were associated with delayed discharge from PICU, and also reported an association of T3 levels with duration of mechanical ventilation [26].

- ❖ Regarding sepsis parameters, FT3 levels were negatively correlated with CRP.

In 2012, Dilli and Dilmen reported that serum FT3 levels were negatively and strongly correlated with CRP in septic patients [30]. This could be explained by the fact that CRP is inducable by cytokines, especially by IL-6, which could also suppress the iodothyronine 5′-deiodinase which mediates the conversion of T4 into T3 resulting in low T3 levels [8]. These findings could be explained by the fact that the severity of NTIS has been associated with poor clinical outcomes of critical sicknesses [31]. Also, some studies indicated that decreased caloric intake during critical sickness is associated with more pronounced NTIS changes [4].

Specifically considering NTIS components, FT3 and rT3 follow-up data, in D-1 and D-5 of sickness, the following observations were obtained:

In our patients, we observed that NTIS extended with worsing of the condition in day 5 compared to day 1; where we observed that FT3 levels were significantly lower and rT3 levels were significantly higher in day 5 of sickness. Furthermore, in non-surviviors FT3 levels in day 5 were significantly lower, and rT3 levels in days 1 and 5 were significantly higher compared to survivors. Although the mechanisms for the elevation of rT3 levels remain uncertain, we could conceive that they are similar to those involved in NTIS pathogenesis [12]. One mechanism that could explain the isolated elevation of rT3 levels in D-1 is drop of its clearance in the liver that appears earlier, also leading to a fall in the FT3 levels. The low half-life of rT3 (around 3 h compared to 24 h for T3) makes rT3 a sensitive and earliest marker for acute changes in thyroid hormones' metabolism [32]. Similarly, Hosny et al. 2015 found that only FT3 levels measured during follow up in day 5 was significantly decreased in non-survivors than survivors [33]. Also, Peeters et al. 2005 found significantly lower levels of T3, T4, and TSH in non-survivors only after 5 days from admission [34]. In contrast to our findings Hulst et al., 2005 found that in older children there was significant increase in T3 levels in day 4 and day 6 after admission when compared to admission levels, while levels of rT3 decreased significantly from admission to day 4 and from admission to day 6 [35]. The probable explanation of our findings could be that the decrease in serum thyroid hormone levels is a dynamic process, which develops over time. Hence, the adaptations of the thyroid axis could be delayed. Furthermore, it was probable that the stress response in our patients has not resolved yet, and the return to anabolism was not completed in day 5 of sickness. Besides, our patients showed sickness progression in day 5 confirmed by significance of SOFA score and CRP in day 5 of sickness in non-survivors than survivors.

As regards prediction of mortality

In our study, we found that FT3 levels in day 5 was the only independent predictor of mortality among the thyroid function tests, as indicated by the largest AUC of (0.847) followed by SOFA score with AUC (0.837). These findings were consistent with results in adults in the study by Hosny et al. 2015 who suggested that FT3 levels in day 5 were the only predictor of mortality among all components of thyroid hormones [33].

In conclusion, NTIS is common among critically ill children and significantly higher among septic shock group than sepsis, but it has variable presentations. Also, Thyroid hormone changes have a prognostic value in predicting mortality among critically ill children with sepsis and septic shock. Beside SOFA score, FT3 measured in day 5 of sickness and were the best predictors of PICU mortality. Further studies on larger numbers of cases are necessary to confirm these observations. More frequent assessments of NTIS are needed along course of sepsis and septic shock.

This study had some limitations, first, the small sample size, second, patients in PICU receive many drugs that might affect thyroid hormone levels. Third, some patients could have sub clinical abnormal thyroid functions before the onset of sickness, which could affect the results.

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Authors' contributions
Tarek Ahmed Abdelgawad put the idea of the study, study design, shared in study supervision and revision of manuscript. Rana A.A. Mahmoud performed data analysis and interpretation, managed the literature searches, and wrote the first draft of the manuscript. Safaa Yossef Abd Elhameed Ali shared in putting the study concept, design, collected the data and mnaged literature searches. Sondos Mohamed Magdy shared in analysis of data and study supervision. Sara Ibrahim Abdelfatah Taha shared in supervision of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study gained approval of the Research Ethics Committee at the Faculty of Medicine, Ain Shams University FMASU MS 47/ 2021 with Federal Wide Assurance No. FWA 000017585 before being carried out. An informed consents were taken from each patient's legal guardian before study enrolment.

Consent for publication
Institutional consent form was used.

Competing interests
The authors declare that they have no competing interests.

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