Original Article

To study thyroid hormone levels (FT3, FT4, and TSH levels) in critically ill children and their correlation with disease severity and clinical outcome in Rajendra Institute of Medical Sciences, Ranchi, Jharkhand

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Abstract

Introduction: There are manifold effects on neuro-endocrine and metabolic systems due to critical illness. Abnormalities in thyroid hormone levels in a critically-ill patient with no pre-existing hypothalamo-pituitary-thyroid dysfunction is seen in Euthyroid sick syndrome or Non thyroidal illness syndrome.The understanding of different endocrinal changes in acute phase of critical illness may help us to intervene early and improve by pharmacological intervention. **Materials and Methods:** Critically ill children admitted in PICU, RIMS,Ranchi, aged 29 days to 17 years. **Results:** In our study, it was seen that FT3 and FT4 were low at admission at admission in critically ill children. And among them, the non-survivors had significantly lower values compared to survivors. **Discussion:** Among this critically ill patient, more than 70% of patients have shown low free T3 (Type I NTIS) and around 50% of low free T4 levels and free T3 levels (Type II NTIS).We have done this study to assess the thyroid dysfunction in critically ill children admitted in our PICU and its correlation with disease severity and clinical outcome.

Keywords: Children, critically ill, thyroid hormone

Introduction

Family medicine practitioners often treat children with illnesses, but with this study, they can correlate with the level of thyroid hormone and can take appropriate measures to save the life of a child. Pediatric critical illness is often unexpected and accompanied by the presence of acute, life-threatening multi-organ dysfunction with the requirement of support to failing vital organs and can occur due to multiple causes like major trauma, extensive surgery, burn injury, and severe medical illness.[1]

There is a period of physiological deterioration often followed by critical illness. Even after a few days of intensive care, if there is no improvement, then the vital organs may need the support of weeks to recover.

There are manifold effects on neuroendocrine and metabolic systems due to critical illness. Mainly, hypothalamic-pituitary axis hormones and autonomic nervous system hormones are affected, and they enact the neuroendocrine response seen in critical illness.[2,3]

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The neuroendocrine response in critical illness is biphasic. The first phase starts within minutes to hours of a major insult. In this phase, there is a catabolic state which is marked by increased release of cytokines, catecholamines, and stress hormones which helps for a fight-or-flight response. These responses increase lipolysis, proteolysis, and gluconeogenesis, and the energy consumption is redirected to those processes that help the individual in acute survival. Anabolism is postponed for a stable period.[4,5]

This survival is provided by taking care of the patient in a critical care unit by providing support to vital organs to cope with this immediate acute stress on the body. In the chronic phase, there is mainly alteration in central and peripheral hormones due to maladaptation, and the patient requires support to the vital organ for a prolonged period, even when the original disease has long been resolved.

Among such changes, one of the commonly encountered endocrinological changes in critically ill patients is Euthyroid Sick Syndrome (ESS) or Non-Thyroidal Illness Syndrome (NTIS) due to changes in the thyroid axis.

Abnormalities in thyroid hormone levels in a critically-ill patient with no pre-existing hypothalamic-pituitary-thyroid dysfunction are seen in Euthyroid sick syndrome or Non-thyroidal illness syndrome. In NTIS/ESS, there is decreased serum triiodothyronine level, and decreased thyroxine level without increased thyroid-stimulating hormone. It reverts back to normal after recovery from the non-thyroidal illness.[1]

The course of critical illness in children differs from adults. A child may develop critical illness quickly, and if he/she survives acute stress, there may be a rapid recovery.

The understanding of different endocrinal changes in the acute phase of critical illness may help us to intervene early and improve by pharmacological intervention, and these endocrine and metabolic changes in critical illness can be used as prognostic markers.

This prompted us to study: Serum thyroid hormone levels (FT3, FT4, and thyroid-stimulating hormone (TSH)) in critically ill children and their correlation with disease severity and clinical outcome.

Materials and Methods

Study area

Pediatric Intensive Care Unit, Department of Pediatrics, Rajendra Institute of Medical Sciences, Ranchi.

Study population

Critically ill children admitted to pediatric intensive care unit (PICU), aged 29 days to 17 years.

The number of subjects fulfilling the inclusion criteria in this study was 112.

Study design

Prospective cohort study design.

Study period

12 months (June 2020–May 2021)

Parameters to be studied

1. Detailed history and clinical examination
2. Thorough investigation including CBC, RFT, ABG, PT, aPTT, serum electrolytes, LFT, RBS
3. Thyroid profile: FT3, FT4, and TSH.

Inclusion criteria

1. Informed consent
2. Age 29 days to 17 years
3. Children admitted to PICU in RIMS, Ranchi, Jharkhand
4. The patient must be enrolled within 24 hours of meeting eligibility admission.

Method of collection of data

Free T3, Free T4, and TSH levels were estimated twice in critically ill patients.

Sample 1: At admission to PICU.

Sample 2: At discharge from PICU or if the patient's condition worsens like prior to death.

FT3, FT4, and TSH levels were measured using the chemiluminescent immunoassay system.

Results

In our study, 112 children who met with inclusion criteria were enrolled in the study, out of which 100 children were included in the study, and the remaining 12 children in whom the second sample could not be obtained due to unavoidable consequences, were excluded.

Statistical analysis was done on the remaining 100 children, and the results are presented as follows:

Age

In our study, 100 children were studied, out of which the majority belonged to the age group more than ten years (121 months–215 months), i.e., 45% as shown in Table 1.

In our study, the majority of the population belonged to the age group of more than 120 months (45%) and toddlers (1–3 years) (18%) group contributing to a total of 63% of our study sample.

Diagnosis

In our study, as shown in Tables 2 and 3, the central nervous system constitutes the maximum amount of PICU admission,

Table 1: Age distribution of study participants

Age (months)	Number	Percentage
2-12	11	11
13-36	18	18
37-60	16	16
61-120	10	10
>121	45	45
Total	100	100

Table 2: Diagnosis distribution of study participants

Disease	Number of patient
Acute encephalitis syndrome	10
Japanese encephalitis	5
Bacterial meningitis	5
Tubercular meningitis	9
Status epilepticus	2
Acute hepatitis with hepatic encephalopathy	7
Acute fulminant liver failure with dic	4
Sepsis	14
Complicated malaria	5
Bronchopneumonia	13
Snake envenomation	8
Organophosphorous poisoining	4
Congenital heart disease in shock	2
Acute lymphoblastic leukaemia	3
Mis-c	2
Severe acute malnutrition with sepsis	1
Hanging	2
Tension pneumothorax	1
Acute glomerulonephritis with aki	1
Dengue	1
Seizure disorder with drowning	1
Total	100

Table 3: System-wise diagnosis with the outcome (*n*=100)

	Non-survivor		Survior		Total	
	n	%	*n*	%	*n*	%
Infectious Disease	8	23.5	11	16.6	19	19.0
Central Nervous System	10	29.4	22	33.3	32	32.0
Hepatobiliary	3	8.8	8	12.1	11	11.0
Respiratory system	4	11.8	10	15.1	14	14.0
Poisoning	2	5.9	10	15.1	12	12.0
Haematology	1	2.9	2	3.0	3	3.0
Miscellaneous	6	17.6	3	4.5	9	9.0
Total	34	100.0	66	100.0	100	100.0

i.e., 32 participants got admitted with central nervous system (CNS) infection (32%), among which Acute Encephalitis Syndrome (AES) was the leading cause, followed by infection and respiratory system illness.

Prism score

It was seen in our study, as shown in Table 4, that children who succumbed to their illness had high Pediatric Risk of Mortality (PRISM) scores at admission with a mean = 35.32 and standard deviation (SD) = 9.936 compared to surviving children who had low PRISM scores on admission with a mean = 13.40 and SD = 6.418 with a *P* value of < 0.0001, which is statistically significant.

Thyroid profile at admission

Free T3: In our study, as shown in Table 5, it was seen that FT3 and FT4 were low at admission in critically ill children. And among them, the non-survivors had significantly lower values compared to survivors.

The mean value of FT3 was significantly lower at admission among the non-survivors (1.39) compared to the FT3 value in survivors (2.22), and a *P* value of < 0.0001 was seen, which is statistically significant.

The mean value of FT4 was significantly lower at admission among the non-survivors (0.67) compared to the FT4 value in survivors (1.01), and a *P* value of < 0.0001 was seen, which is statistically significant.

The mean value of TSH was within normal values in both non-survivors (2.84) and survivors (2.65) with a *P* value of 0.5015, which is not statistically significant.

Thyroid profile at discharge

In our study, as shown in Table 6, it was seen that FT3 and FT4 were low at discharge in critically ill children. And among them, the non-survivors had significantly lower values compared to survivors. The comparision of thyroid level at admission and discharge in shown in Table 7.

In our study, it was seen that among non-survivors, FT3 and FT4 were low at admission while TSH was within the normal limit, as shown in Table 8.

The mean value of FT3 in non-survivors has shown a decrease in values from admission (1.39) to discharge (1.22), and the mean value of FT4 non-survivors has shown a decrease in values from admission (0.67) to discharge (0.62). The mean value of TSH in non-survivors has shown a decrease in values from admission (2.84) to discharge (2.27).

Thyroid profile with prism score

In our study, as shown in Table 9, it was seen that there is a small negative correlation between thyroid profile (FT3 and FT4) and PRISM score at admission, which was statistically significant. Trivial correlation between TSH and PRISM score at admission with the *P* value of 0.4832 is statistically insignificant. Also, it was seen that there is a large negative correlation between FT3 levels at discharge with a PRISM score with *P* value of < 0.0001 and a moderate negative correlation between FT4 levels at discharge and PRISM score with a *P* value of < 0.0001.

Table 4: Prism score of study participants (*n*=100)

	Survivor	Non-survivor
Mean	13.40	35.32
Median	12	34
Minimum	3	21
Maximum	32	60
Standard deviation	6.418	9.936

P<0.0001, statistically significant; unpaired *t*-test by Welch's correction

Table 5: Comparison of thyroid profile at admission based on the outcome of the study participants (*n*=100)

	Non-survivors Mean (SD)	Survivors Mean (SD)	*P**
Free T3	1.39 (0.21)	2.22 (0.96)	<0.0001
Free T4	0.67 (0.27)	1.01 (0.39)	<0.0001
TSH	2.84 (1.29)	2.65 (1.65)	0.5015

Table 6: Comparison of thyroid profile at discharge based on outcome of the study participants (*n*=100)

	Non-survivor Mean (SD)	Survivor Mean (SD)	*P*
Free T3	1.22 (0.18)	3.01 (0.83)	<0.0001*
Free T4	0.62 (0.49)	1.68 (1.09)	<0.0001*
TSH	2.27 (1.70)	3.68 (3.87)	0.0513**

*Mean value of FT3 at discharge was significantly lower among non-survivors (1.25) compared to survivors (3.00), with a *P* value seen <0.0001, which is statistically significant. *Mean value of FT4 at discharge was significantly lower among non-survivors (0.68) compared to survivors (1.64), with a *P* value seen <0.0001, which is statistically significant. **Mean value of TSH at discharge was within the normal range among non-survivors (2.80) and among survivors (3.55), and a *P* value of 0.0513 was seen, which is statistically insignificant

Table 7: Comparison of thyroid profile between admission and discharge among survivors (*n*=66)

	At admission Mean (SD)	At discharge Mean (SD)	*P**
Free T3	2.22 (0.96)	3.01 (0.83)	<0.0001
Free T4	1.01 (0.39)	1.68 (1.09)	<0.0001
TSH	2.65 (1.65)	3.68 (3.87)	0.15

Discussion

Among the critically ill patients, more than 70% of patients have shown low free T3 (Type I NTIS), and around 50% of low free T4 levels and free T3 levels (Type II NTIS).[6] We have done this study to assess the thyroid dysfunction in critically ill children admitted to our PICU and its correlation with disease severity and clinical outcome.

In our study, a total of 100 critically ill children with a mean age of 97 months and 64% of the male child were studied. PICU admission of our study participants was mainly due to central nervous system causes (32), followed by infectious disease (19%), then respiratory causes (14%).

The mean PRISM score of our study was 23.3 ± 16 points. Higher PRISM score reflects severe disease with higher mortality risk in patients. The mean PRISM score in survivors was 13.4 ± 6.4 and in non-survivors, it was 35.32 ± 9.9 with a *P* value of < 0.0001. Thus, our study showed that higher PRISM scores at the admission of patients had more severe diseases and higher mortality risk. A study conducted by **Roshani** *et al.* **(2010)**[7] concluded that the PRISM score has a good discriminatory performance, and the calibration with the PRISM score is good.[6]

On the basis of the normal ranges mentioned above, the commonest change seen in our study was low serum FT3 level in 67% of cases, followed by low FT4 levels in 40% of cases, and 9% of patients had high TSH at admission. In a study conducted by **Wang** *et al.*[8] in 480 critically ill patients showed that 261 (54.38%) and 48 (10.00%) patients had low FT3 and low FT4 levels, respectively, and 17 (3.54%) had high TSH levels.

In our study, a large number of ESS type 2 cases (40%) were found, and it showed that low FT3 and FT4 was a predictive marker for disease severity and poorer outcome in critically ill patients.

In our study, it was also noticed that the FT3 and FT4 levels (1.22 ± 0.18 and 0.62 ± 0.49) were significantly low at discharge in non-survivors than when compared with survivors with a *P* value of < 0.0001.

Serum FT3 and FT4 level improved on discharge from the PICU and did not improve in those who expired, which indicates that serum FT3 levels closely follow the clinical condition, and a low level may correlate with poor outcome.

Serum FT3 levels are also decreased in patient prior to death which indicates that although serum FT4 level at admission did not discriminate between cases that expired or recovered, it decreased in patients prior to death, reflecting the seriousness of the disease. FT4 level is maintained in severe illness due to increased secretion from the thyroid gland, but in very severe illness, the FT4 level fails to maintain due to accelerated turnover and level decreases.[9]

In patients with different phases of critical illness, the levels of T4, FT4, and TSH may be variable, but the T3, FT3 level is generally reduced, and hence it is better than T4 and TSH level for predicting outcome in the pediatric intensive care unit.

In our study, it was demonstrated that the addition of FT3 and FT4 levels to PRISM III scores could significantly improve the ability to predict the disease severity and PICU mortality.

The pathophysiological mechanism underlying the association of lower FT3 and FT4 levels with worse outcomes in PICU patients has yet to be fully defined. It is still unclear whether the alteration in thyroid hormone levels during critical illness is the adaptive physiological response to stress or the maladaptive response requiring treatment.[10]

Table 8: Comparison of thyroid profile between admission and discharge among non-survivors (*n*=34)

	At admission Mean (SD)	At discharge Mean (SD)	*P**
Free T3	1.39 (0.21)	1.22 (0.18)	<0.0001
Free T4	0.67 (0.27)	0.62 (0.49)	0.1033
TSH	2.84 (1.28)	2.27 (1.70)	0.2337

Table 9: Correlation of thyroid profile with prism score (at 24 hr)

	r	*P*
At admission (*n*=100)		
Free T3	–0.2857	0.0040
Free T4	–0.2613	0.0086
TSH	0.07092	0.4832
At discharge (*n*=100)		
Free T3	–0.5640	< 0.0001
Free T4	–0.3913	< 0.0001
TSH	–0.05505	0.5804

Conclusion

The non-thyroidal illness syndrome (NTIS) refers to changes in the serum thyroid hormone levels (FT3 and FT4 mainly) observed in critically ill patients in the absence of hypothalamic-pituitary-thyroid primary dysfunction. The mean FT3 and FT4 levels in critically ill children are low. On recovery, the thyroid hormone levels normalize; however, low level of FT3 or/and FT4 persists or worsens in case of death. At admission to the PICU, FT3 and FT4 levels are low along with or without high TSH in children who will subsequently die, and therefore, more aggressive therapy may be warranted in such children. In critically ill children, the peripheral inactivation of thyroid hormone is characterized by a decrease in T3/rT3.[6] Patients with low levels of FT3 had a high mortality rate.[11]

Key points: At any given point, FT3 and FT4 level reflect the patient's clinical status, and persistent low serum T3 levels with non-improvement would spell a bad prognosis. Patients with combined low T3 and T4 levels have an increased risk of mortality.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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