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Original Article

Alterations of Thyroid Function in Critically Ill Children

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ABSTRACT

Title-Alterations of thyroid function in critically ill children

Aims & Objective- To study thyroid hormonal changes in critically ill children and correlate them with outcome.

Methods-In this prospective study total serum T_3, $T_4$and TSH levels were estimated at admission and at discharge or prior to death in fiftycritically ill cases admitted to PICU.Fifty healthy children were taken as controls. PRISMII score was used to predict outcome. Hormone levels were compared between cases and control and then between survivors and non survivors.

Results- Mean T_3 (59.86±16.09 vs123.04±26.21)and T_4 levels (5.38±1.30vs8.70±1.82) in cases were significantly (P-0.000) lower than that of controls,however no significant difference in the mean TSH values (2.21±1.91 vs2.18±1.06) were noted. Fourteen (28%) cases expired. Admission T3 level (44.71±13.35 Vs65.75±13.01) was significantly (p-0.000) lower in non survivors than survivors but there was no significant difference in T4 (4.86±1.57Vs5.57±1.15) and TSH(2.17±1.69 Vs 2.28±2.12) levels. Serum T_3 (65.75±13.01vs96.36 ±25.48),T_4 (5.57±1.15vs8.52±3.19) and TSH levels(2.28±2.12 vs3.06±1.61)improved in survivors butfailed to improve innon survivors. LowT3 and T4 at admission were associated with high risk of mortality (odds ratio 14.8, p-0.000). PRISMII score and T4 in second sample were significant predictors of death.

Conclusion-In critically ill children T3, T4 levels are low, while TSH values may not change. T3 levels reflect patient's clinical status and T4 levels can predict death.

Key words- thyroid hormone, critically ill children, PRISMII

Introduction

Altered thyroid function in nonthyroidalillness(NTI) is a well-recognized finding [1,2]The term euthyroid sick syndrome (ESS) identifies abnormalities in thyroid function tests observed in patients with systemic nonthyroidal illnesses (NTIs).ESS has been classified as Type 1- low T_3 syndrome, Type 2-low T_3&low T_4 syndrome and Type 3-low TSH syndrome. The severity and the nature of changes in thyroid function test have implications for the prognosis of the systemic illness.[3,4]These abnormalities result from variable, usually reversible, disturbances in the hypothalamo-pituitary-thyroid axis, thyroid hormone binding to serum proteins, tissue uptake of thyroid hormones, and/or thyroid hormone metabolism.[5]

The production of thyroxine (T4) by the thyroid gland is regulated by the classic hypothalamus-pituitary-thyroid axis, in which the anterior pituitary releases thyroid stimulating hormone (TSH) thyrotropin as a result of the stimulation by hypothalamic thyrotropin-releasing hormone (TRH). The biological activity of thyroid hormone (i.e. the availability of the active hormone 3,5,3 V-triiodothyronine [T3]), is largely regulated by the iodothyroninedeiodinases D1, D2, and D3 which convert T4 to either T3 or to the inactive metabolite reverse T3 (rT3). Both T4 and T3 have an inhibitory effect on TRH and TSH secretion by way of a negative feedback loop mechanism.[5,6]

Low serum total T_3 is the most common abnormality

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in NTI. It is observed in about 70% of hospitalized patients.[7] Serum total T_3 may vary from undetectable to normal in patients with systemic illness.Within a few hours after the onset of disease, plasma T3 decreases and plasma rT3 increases, and the magnitude of these reciprocal changes is related to the severity of the disease.[7-9]Altered expression of thyroid hormone transporters, impairment of 5' deiodinaseactivity due to reduced availability of the enzyme co-factorglutathione due to reduced intake of carbohydrates, stress induced elevated steroids and free fatty acids as inhibitor of extra-thyroidal T4 to T3 conversion are some of the postulated mechanisms. [10-13]

T4 decreases as well with T3 in severely ill patientsand both low T4 and low T3 are associated with a poorprognosis.[14-16] Suppression of thyroid releasing hormone (TRH) from hypothalamus due todysregulation or inhibitory action of somatostatin,decreased pituitary response to TRH,decreased pituitary secretion of TSH due to cortisol, growth hormone, dopamine, opiate peptides secreted in response to stress, decreasedresponsiveness of pituitary TSH to low T3 or T4 and reduced plasmabinding of T4 are suggested reasons for low T4.[17-20]

Majority of the studies till date on thyroid function test and its correlation with outcome in critically ill patients are mainly conducted in surgical ICUs especially in adults. There is paucity of data available in pediatrics ICUs, especially in India on this subject. Hence present study was conducted to evaluate the alteration of thyroid hormone function in critically ill children and to assess its correlation with their outcome.

Materials and Methods

In this prospective study fiftycritically ill children admitted in Pediatric intensive care unit (PICU) were studied over a period of 1.5years (august 2010 to february2012). Critical illness was defined as any condition leading to malfunction of one or more organ system requiring support to maintain vital functions either with mechanical or pharmacological aids. PRISMII score (Pediatric risk of mortality score) was used to predict the outcome in critically ill patients at 0 and 24 hours. Data was collectedwithin first hour of admission to pediatric ICU. Data collection pertinent to the analysis included ICU admission diagnosis, categorized by primary physiologic instability and outcome (survival or death). Total serum T3,T4,TSH levels were estimated twice in critically ill patients,first sample at admission to PICU and second sample at discharge or prior to death (depending on the outcome ofpatient).Fifty age and sex matched healthy children were taken as controls.

Admissions for post procedure recovery, cases with maternal or family history of thyroid illness,clinical evidence of thyroid dysfunction, or patients on any thyroid medication or on long term glucocorticoids, patient on drugslike radiographic agents,amidarone and propranolol which affect directly thyroid functionwere also excluded from the study. The data was recorded on standardized sheet and included demographic variables such as age, sex, outcome, T3, T4, TSH levels and 14 physiological variables used in PRISMII score.Estimation of variable parameters was done. Blood pressure was recorded withnoninvasive multipara monitors and oxygen saturation measured with pulse oximeter at admission. The Fio2 required formaintaining oxygen saturation above 90% was noted with oxygen monitor. Radial artery sampling was used for determining Pao2, Paco2 and bicarbonate levels. Standard lab techniques were utilized to measure blood levels of total bilirubin, protein,potassium, calcium, glucose, prothrombin time and partial thromboplastin time. Clinical assessment of heart rate, respiratory rate and pupillary reaction for each patient was made. The children were followed up during the hospital stay and the outcome measures were recorded as deathor survived at the end of hospital stay.Serum total T_3, T_4 & TSH levels were estimated by solid-phase competitive luminescence immunoassay (CLIA). T3 values less than 60 ng/dl, T_4 values less than 4.5 mcg/dl & TSH values less than 0.3 uU/ml was considered as lowT3, T4 & TSH values respectively. Cases were also classified as Type I, Type II & Type III Euthyroid sick syndrome (ESS) accordingly. Only low T_3 as ESS Type I, both Low T_3 & Low T_4 as ESS Type II & Low TSH as ESS Type III.

The hospital ethics and review board's approval and informed consent from relatives was taken before undertaking the study. Statistical analysis of data was done by using IBM SPSS 19.0 Statistics software. Normally distributed continuous variables were compared with Student's t-test and categorical variables were compared with Chi-square test or Fisher's exact test. Pearson Correlation coefficient was used to study bivariate correlation. After determination of individual factors with mortality by univariate analysis, a binary logistic regression model of significant factors associated with mortality was developed. The results of regression model were presented as adjusted odds ratio. Wald's chi square value was used to test unique contribution of each predictor. Regression model adequacy was tested by Omnibus test of model coefficients, Negelkerke R square and Hosmer&Lameshow chi square test. Receiver Operating Characteristic Curve analysis was used to find out the cut-off values for T, T4 and TSH and for PRISM II score to validate predicted probabilities of death.P< 0.05 was considered statistically significant.

Results

Mean age of fifty critically ill children inthe case group was78.92±40.78 months (range14 to 156 months).There was no significant difference in mean values of T3(60.28± 17.69 Vs.57.12 ±12.71ng/dl), T4(5.64±1.05 Vs. 5.41±1.25mcg/dl) and TSH (2.53±1.25Vs2.24±1.61) between males and females. The distribution of cases according to diagnosis is mentioned in Table 2.Mean total protein levels (5.49±1.67 vs.6.01±0.66 gm) were comparable between cases & controls. Fourteen (28%) children died and 36 (72%) survived. The means and SD of thyroid profile for given sample size and alpha (0.05,2 tailed), power of study was 1.00. The average duration between the first and second sample in survivors was 7.64 ± 2.08 days and in non survivorscases was 6.29 ± 2.28 days.

Mean serum T3 and serum T4 levels were significantly lower in cases than that in controls. Howeverserum TSH levels were not significantly different betweentwo groups (Table 1). At admission there was no significant difference in the serum levels of T4 and TSH between survivor and non survivors. However serum T3 level was significantly lower in non survivors (Table 3). Among survivors T_3, T_4 and TSH levelsat discharge showed significant (p-0.000) rise as compared to their admission levels. However T_3, T_4 and TSH levelsin the non survivors failed to improve (Table 4). There was no significant difference inmean total protein levels (5.78±0.62 Vs 5.38±0.66) between survived and expired children.

Table1: Comparativedemography in cases verses controls

Parameter	Cases (*n*=50)	Controls (*n*=50)	*P*value
Male/female	37/13	38/12	0.817
Age in months	78.92±40.78	81.02±41.17	0.798
Serum proteins	5.49±1.67	6.01±1.66	0.126
T3	59.86±16.09	123.04±26.21	0.000
T4	5.38±1.30	8.70±1.82	0.000
TSH	2.21±1.91	2.18±1.06	0.928

Table 2: Distribution of cases according to diagnosis

Diagnosis	Cases (*n*=50)	Deaths (*n*=14)
Viral encephalitis	7 (14%)	3 (21.4%)
Status epilepticus	3 (6%)	0
Congestive cardiac failure	8 (16%)	2 (14.3%)
Severe acute asthma	7 (14%)	2 (14.3%)
Acute renal failure	3 (6%)	1 (7.14%)
gastroenteritis	6 (12%)	1 (7.14%)
Septic shock	10 (20%)	3 (21.4%)
Trauma	6 (12%)	2 (14.3%)

Table 3: Comparison of thyroid profile between survivors & non survivors

Parameter	Survivors (*n*=36)	Non survivors (*n*=14)	*P*value
First T3	65.75±13.01	44.71±13.35	0.000
First T4	5.57±1.15	4.86±1.57	0.085
First TSH	2.28±2.12	2.17±1.69	0.093
Second T3	96.36±25.48	42.57±11.94	0.000
Second T4	8.52±3.19	3.58±1.74	0.000
Second TSH	3.06±1.61	2.23±1.67	0.113
PRISM II at admission	7.17±1.78	8.64±1.73	0.011
PRISM II at 24hrs	7.50±1.75	10.79±1.72	0.000
Serum proteins	5.78±1.62	5.38±1.34	0.416

PRISMII: Pediatric Risk of Mortality Score II

Low T3 alone (type I ESS) was seen in 32 (64%) children, mortality in this group was 37.5% (12 out of 32) (odds ratio 4.1,p=0.056) while a combination of low T3 and T4 (type II ESS) was seen in 13 (26%) cases with mortalityof 69.23% (9 out of 13) in this group and demonstrated almost 15 times more risk of mortality (odds ratio 14.9, p<0.000). Only 3 (6%) cases had isolated low TSH (typeIII ESS) & 2 (4%) had lowT4 alone. There was no death inType III ESS group.

Table 4: Comparison between the thyroid parameters in the first and second samples

Parameter	survivors	*P*value	Non survivors	*P*value
First T3	65.75±13.01	0.000	44.71±13.35	0.000
Second T3	96.36±25.48		42.57±11.94	
First T4	5.57±1.15	0.000	4.86±1.57	0.000
Second T4	8.52±3.19		3.58±1.74	
First TSH	2.28±2.12	0.000	2.17±1.69	0.065
Second TSH	3.06±1.61		2.23±1.67	

PRISMII score at 24 hrs.was significantly higher in patients who expired (10.79±1.72 Vs 7.50±1.75,p= 0.000). PRISM score at 24 hours did not correlate with T3, T4 or TSH levels at admission, but had negative correlation with T4 levels of the second sample (Table 5). Age, sex, duration of PICU stay, ventilation and inotropic support did not show any correlation with patient outcome or thyroid hormone profile.

Table 5: Correlation of Thyroid Profile with PRISMII score & duration of PICU stay

Parameter	PRISMII at 24hrs		PICU stay	
	r	*P*value	r	*P*value
First T3	-0.037	0.953	-0.213	0.138
First T4	-0.734	0.068	-0.127	0.379
First TSH	-0.046	0.931	0.045	0.755
Second T3	-0.129	0.806	0.001	0.995
Second T4	-0.864	0.038	0.075	0.460
Second TSH	-0.090	0.864	0.201	0.286

r=correlation coefficient

Table 6: Multivariate analysis of factors associated with mortality by logistic regression

Variable	Wald	S. E	df	P value	Odds ratio
Second T4	5.338	0.252	1	0.021	0.558
PRISM II at 24 hrs	4.192	0.290	1	0.041	1.811
constant	-0.3186	0.963	1	0.327	0.041

PRISMII: Pediatric Risk of Mortality Score II, SE-standard error, df: Degree of freedom

The area under Receiver Operator Characteristic (ROC) curve for the various thyroid hormone parameters, PRISMII score at admission and 24 hrs. with death as classification variable, along with the sensitivity and specificity is listed in table 7. The values for Area under curve (AUC) for second T4 (0.932) was comparable for PRISMII score (0.907) [Table 7] [Fig 1]. As AUC for second T4 for had highest sensitivity & specificity closely matching with respective value of PRISMII score, T4 as an

Table 7: ROC curve analysis of factors associated with mortality

Variable	AUC	SE	Pvalue	95%CI	sensitivity	speci city	criterion
First T3	0.883	0.0724	0.001	0.761to0.956	85.7%	91.7%	≤ 51
First T4	0.705	0.0986	0.032	0.560 to0.826	64.3%	88.9%	≤ 4.45
First TSH	0.526	0.0905	0.779	0.380 to 0.669	57.1%	63.9%	>1.91
Second T3	0.867	0.0873	0.001	0.741 to0.946	78.6%	94.4%	≤ 46
Second T4	0.932	0.0431	0.000	0.823 to 0.984	92.9 %	83.3%	≤ 4.4
Second TSH	0.679	0.100	0.742	0.532 to0.804	42.9 %	75.4%	>0.91
PRISMII admission	0.735	0.0795	0.002	0.591 to 0.850	71.3 %	66.7%	> 7
PRISMII 24hrs	0.907	0.0401	0.000	0.790 to 0.971	92.9%	77.8%	> 8

ROC-receiver operting charateristic, AOC-area under curve, SE-standard error, CI-confidence interval

independent risk factor for mortality was studied by multivariate analysis using forward stepwise method of binary logistic regression. PRISM score at 24 hrs. And T4 levels in second sample were found to be significant predictors of mortality; (Table 6). Values of Omnibus model coefficient(33.58.p-0.000 at df=2) Nagelkerke R square (0.704) and Hosmer & Lemeshow test (chi-square 9.11 at df-8, sig.0.333) indicated strong predictive value & overall fitness of the regression model. Other thyroid hormone parameters were not found to predict mortality significantly.

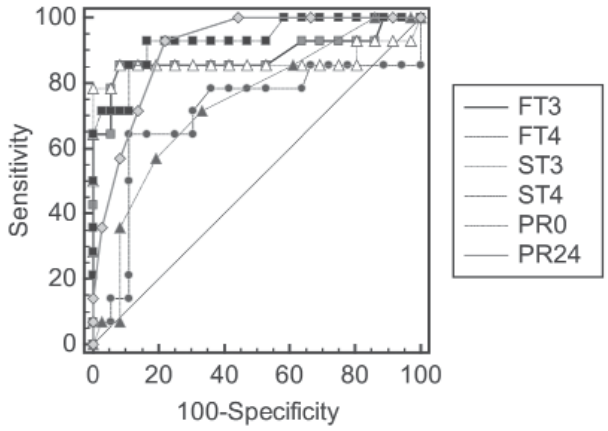

Figure 1: Comparison of ROC curve

Discussion

Present study demonstrated lowermean T3 and T4 levels in the critically ill children. The commonest change seen was reduced serum T3 level (64% of cases). Low T4 levels were seen in 30% of cases,while low serum TSH level in only 6%of cases. Similar pattern was observed by Suvarna et al.[25] Many studiesreported ahigher incidence of lowT3 levels in critically ill patients[14,22,24,25]but Bermudez et al[7] in their study on adult patients and Anand et al[21] in their study on critically ill infants failed to demonstrate significant lower serum T4 levels.

The combination of low T3 & low T4 was associated with almost 15 times risk of mortality in the present study. Similar observation was demonstrated in Zargar et al & Suvarna et al. [14,25]However, further multi-centric studies with larger sample size may throw more light on this aspect.

The serum T3 levels at admission has been considered as baseline discriminator between survivors and non-survivors, which can prognosticate the clinical status ofcritically ill patients.[15]In the present study the mean serum T3 levels at admission was lower in nonsurvivors. Though Zucker et al & Suvarna et al [24,25] had similar observation, Anand et al & Uzel et al failed to demonstrate the same in infants [21,22] It was also noted that serum T3 level improved in patients discharged from the PICU and did not improve in those who expired. This implies that serum T3 level closely follows the clinical status of the patients and persistently lowserum T3 level may reflect poor outcome.

Although serum T4 level at admission did not discriminate between survivors and non-survivors, it decreased in patients prior to death reflecting the seriousness of the disease. It is postulated that when an illness is severe but less than life threatening, T4 levels are maintained due to increased secretion rate to match the accelerated T4 disposal. However, in very severe illness, the T4 level fails to keep up pace with the accelerated turnover and decreases. [17] Wecould not demonstrate any cut-off value for T4 to correlatewith patient's outcome. Zucker et al too failed to show this relationship.[24] Serum T4 levels at discharge from PICU or just prior to death and PRISMII score at 24 hours of admission to the PICU were found to besignificant predictorsof mortalitywith highest sensitivity & specificity. Similar finding was observed bySuvarna et al.[25]

Type II ESSis reported with more severe illness and indicates a very poor prognosis.[15,16] In 26 % cases it demonstrated almost 15 times increased risk of mortality. Suvarna et al[25]reported 30 times risk of mortality in such patients.Thesepatients have inappropriately normal or low TSH inspite of low T3 and T4 and are considered to be clinically euthyroid. Glutathione and selenium are postulated to be co-factors for both enzymes: deiodinase (needed for T4 to T3 conversion) and glutathione peroxidase (defense strategy of the body to combat oxidative stress). Stress (critical illness) decreases the activity of deiodinase, thus sparing the co-factors for glutathione peroxidase activity (to combat stress). [3]Also low T3 decreases catabolism, thus decreasing mitochondrial free radical generation, and allowing

energy to be expended for the defense processes. Thus ESS maybe considered as an adaptive process. (7,8,24,29)

We observed that in patients who survived, TSH levels increased significantly while it failed to improve in patients who expired. Similar observation was found by Suvarna et al.(25)The transient increase in serum TSH during recovery from NTI suggests that TSH is suppressed in an illness. Pituitary TSH suppression may be related to the stress of an illness, and the resulting elevated cortisol and catecholamine levels and associated caloric deprivation.(4)

Almost in all critical illness,there is a decreasein plasma concentration of proteins that bind thyroid hormone [albumin, thyroid binding pre albumin (TBPA) & thyroid binding globulin (TBG)]. As binding proteinsdecrease, total levels of T4 and to lesser degree of T3 decline.(1,3,5) The free thyroxine index (FT4I) is an estimate of the amount of circulating free thyroxine which doesn't get affected by levels of TBG or TBPA and can be used as sensitive indicator to diagnose ESS.(2,3,6) We have not estimated FT4I ,TBPA or TBG in our study due to high cost involved, butas there was no significant difference in total serum protein levels of either cases and controls or between survived and expired, we can presume that changes in thyroid profile were reflecting critical phase of illness and not hypoproteinemia.

'Is there any role of T3, T4 supplementation in critically ill patients inimproving survival?' The improvement of T3 levels in patients who survived and non-improvement in those who expired raises this important question, Most studies perceive low T3 without increased TSH as an adaptive response (metabolically protective) not warranting administration of T3 or T4 in NTI.(20,23,24,28) Moreover decreased deiodinase activity in NTI may hamper peripheral conversion of T4 to T3.(28) T4 therapy may in fact suppress thyroid function normalization during recovery by inhibiting TSH secretion.(28) Administration of T3 in severe burnsdid not affect survival.(17) However T3 infusion in patients with septic shock showed elevation of systolic blood pressure, reduced vasopressor requirement and improvement in renal function.(28) Recent reports showed cardiac surgery patients with ESS tolerated T3 replacement therapy well and showed hemodynamic improvementsin form of increase in cardiac index, reduced need of for inotropic agents and mechanical device and decreased incidence of myocardial ischemia(27) The therapeutic role of thyroid hormones in the management of NTI is still not very clear and awaits further well controlled randomized trials.

Conclusions

In critically ill children,mean T3, T4 levels are low,while TSH values may not change. At any given point T3 level reflects the patient's clinical status and persistent low serum T3 levels with non-improvement would predictbad prognosis. Low T3 & T4 values at admission are associated with very high risk of mortality. T4 levels independently can predict mortality with high sensitivity & high specificity like PRISMIIscore at 24 hours. Children with combined low T3 and T4 levels need more close observation and aggressivetherapeutic intervention.

Limitations:

Confounding bias related to effect of inotropic agents (dopamine, dobutamine) or exogenous steroid used in critical illness on thyroid hormones could not be eliminated. Estimation of rT3 and free T4 was not done in this study which would have given us an additional thyroid indicator of prognostic value.The thyroid hormone profle was done only twice i.e. at admission and at recovery or death in this study. More frequent estimation to assess the trend of changes in the thyroid hormone profle in the sick children can give us better information and help us to identify seriously ill patients much earlier.

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